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Serial changes in the T_1 magnetic relaxation parameter after myocardial infarction in man

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SUMMARY A low field resistive nuclear magnetic resonance imaging system (0·08 Tesla) was used to study the in vivo changes in the relaxation parameter T_1 of the left ventricular myocardium from the first day to six months after acute myocardial infarction in 41 consecutive patients admitted to a coronary care unit. T_1 maps were constructed from transverse and coronal images at various times after infarction. Thrombolytic treatment had been successful in 28 patients. Thirty three of the 34 patients studied within two weeks of infarction had a significantly increased T_1 value but this developed only after the third day in four. At day 1–3 the mean (1 SD) maximum T_1 was 413 (29) ms ($n = 23$) compared with 430 (41) ms ($n = 22$) at day 4–7, 433 (35) ms ($n = 24$) at day 8–14, 420 (34) at one month ($n = 22$), 388 (39) ($n = 20$) at three months, and 361 (24) ($n = 14$) at six months. The number of regions of interest with an increased T_1 followed a similar time course. Although the increase in T_1 measured at three months correlated with the initial maximum creatine kinase and with the left ventricular ejection fraction measured at one month, the number of regions with abnormal T_1 from day 4 through to one month correlated best with left ventricular ejection fraction. There was no significant difference in T_1 between patients with or without reperfusion. The rise in T_1 over the first few days together with the prolonged time course of T_1 increase suggests that the increase in T_1 may reflect cellular infiltration as much or more than tissue oedema.

It has been suggested that the magnetic relaxation parameters T_1 and T_2 which are associated with an increase in free water content may be used to demonstrate tissue abnormalities.[1] After experimental canine myocardial infarction in vitro T_1 and T_2 were prolonged, and these changes correlated well with increases in tissue water content.[2 3] In vivo prolongation of both T_1 and T_2 after myocardial infarction has been confirmed in dogs[4 5] and recently in human beings.[6 7] In dogs the changes begin within 30 minutes of coronary occlusion[2] and become more pronounced with occlusions of one, two, and three hours.[2 5] Recently, Pflugfelder *et al* described the serial changes in the intensity of the in vivo signal in canine myocardial infarction[8] but similar studies in human beings have not been reported.

The purpose of the present study was primarily to define the time course of changes in T_1 after acute myocardial infarction in human beings.

Patients and methods

We studied 41 patients with transmural myocardial infarction that was confirmed by both electrocardiographic and creatine kinase changes. Whenever possible, imaging was carried out on day 1–3, day 4–7, day 8–14 and one month, three months, and six months after infarction. Serial imaging was performed on 2–6 occasions (mean 3·4 per patient); however, in two patients adequate images were obtained on one occasion only. Consecutive patients were selected provided that the imager was available, the patient consented, and none of the following exclusion criteria was present: current symptomatic pulmonary oedema, continuing chest pain, major

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arrhythmia within 12 hours, previous infarction in the same electrocardiographic territory, or any myocardial infarct in the preceding year.

The study was approved by the local ethics review committee and all patients gave written informed consent.

Ten patients did not have thrombolytic treatment and in a further three thrombolysis was found to be unsuccessful at subsequent coronary angiography (group 1). The remaining 28 patients (group 2) had successful coronary thrombolysis with intravenous anisoylated plasminogen streptokinase complex[9] (n = 23) or recombinant tissue type plasminogen activator (n = 5) (table 1).

The study population was heterogeneous in terms of the site of infarct, rise in creatine kinase, and the use and success of thrombolytic treatment (table 1). Patients on thrombolytic treatment underwent early coronary angiography to determine whether the infarct related vessel was patent, and left ventricular function was assessed by gated blood pool scan.[10] In all patients creatine kinase activity was measured twice a day during their stay in the coronary care unit.

The number of patients in group 1 (n = 13) was smaller than that in group 2 (n = 28) because the use of thrombolytic treatment increased during the study and because non-reperfused patients tended to be less well and were therefore more likely to be excluded from this study.

MAGNETIC RESONANCE IMAGING TECHNIQUE

Patients were imaged with a 0·08 T vertical field resistive magnetic resonance imaging system, manufactured by M & D technology, installed in the Edinburgh Royal Infirmary,[11] and situated between the coronary care unit and the angiography laboratory. Calculated T_1 maps were obtained by an interleaved saturation-recovery and inversion-recovery pulse sequence with a time from inversion (TI) of 200 ms. Inversion was obtained with an adiabatic fast passage inverting pulse rather than the usual 180° pulse; this is particularly suitable for precise T_1 calculation because it efficiently inverts all the nuclei within the section. In addition, it is not slice selective, which means that it inverts all the nuclei within the heart and therefore does not have to be synchronised with the cardiac cycle.

Table 1 *Data (mean (1 SD)) on the study population*

	Group 1	*Group 2*
	Coronary occlusion (proven or assumed)	*Coronary reperfusion (proven vessel patency)*
No of patients	13*	28
Anterior infarction	5	19
Inferior infarction	8	9
Age (years)	57 (10)	53 (10)
Peak creatine kinase (U/l)	1889 (800)	1947 (1334)

*Confirmed at angiography[3] or assumed because thrombolysis was not used.

The patient's electrocardiogram was used to trigger the imager such that the 90° pulse in both the saturation-recovery and inversion-recovery sequences occurred in the same part of the cardiac cycle.[12] A field gradient echo of 20 ms was used. The minimum time from the R wave trigger at which imaging can be performed is 230 ms, principally because of the time from inversion (TI) values used. Partly as a consequence of this, but also to obtain tomographic sections of maximum myocardial thickness, images were obtained towards end systole. The pixel size was 3·5 mm × 3·5 mm.

In an attempt to obtain comparable sections on serial studies for individual patients we used the following routine. After attachment of the electrocardiographic leads we used an alignment marker to position the patient on the couch. The lower edge of the xiphisternum was used as the reference level. The distance of subsequent couch movements was recorded from the digital readout provided by the system. Initial images were obtained with a 16 s ungated saturation-recovery sequence as an anatomical guide for the sections to be scanned. Having optimised the image position and recorded its distance from the xiphisternum we performed a gated scan with a slice thickness of 16 mm. To encompass the whole left ventricle, further scans were performed at two or three 15 mm levels cranial or caudal to this or both, and the position was noted to allow equivalent sections to be obtained at subsequent imaging.

A single coronal section through the left ventricle was obtained. The most suitable imaging slice was again selected from rapid ungated images, but in this case the position was adjusted by slightly altering the strength of the magnetic field. Despite the measures described above, it is likely that changing left ventricular geometry over the six month period prevented serial imaging of exactly the same portion of myocardium. For this reason we used the area of highest T_1 found in any region of interest in the infarct territory for analysis.

The imager was triggered by each R wave for heart rates <75/min and by alternate R waves for faster heart rates. Patients who were scanned during the first 48 hours while in the coronary care unit were moved on a trolley equipped with a defibrillator, and electrocardiographic monitoring was continued throughout.

DATA ANALYSIS

For analysis of T_1 values, the myocardium was divided into six sections for each image containing the left ventricular myocardium and cavity. Figure 1 shows the areas into which the myocardium was divided. T_1 values for each of the six sections of every image were obtained by using the computer to draw circular regions of interest within the myocardium. The largest circle that could be placed clearly within the myocardium was used. The area of interest selected was either 0·26 or 0·51 cm^2, but where wall thinning was considerable the smallest available region of interest (0·08 cm^2) was used. This gives a T_1 value of the full thickness of the ventricular wall but with a greater contribution from the central portion of the myocardium. In nine patients there was considerable thinning of the myocardium in the infarct region (eight anterior, one inferior). To avoid the possibility that measurements of myocardial T_1 from this region might be rendered inaccurate by inclusion of intracavitary signal (from blood or thrombus) or extramyocardial signal (from pericardial fat or connective tissue) the region of interest was modified where necessary to encompass the closest lateral position which lay clearly within the myocardium. Attempts at obtaining a T_1 value from the narrowed segment illustrated the necessity for this modification since minor inward or outward adjustment of position resulted in major alterations in T_1.

The maximum T_1 value for each patient investigation was noted as was the number of areas with a T_1 value >390 ms, the value previously identified as the cut off between normal and infarcted tissue.[7] Values for non-affected myocardium were then obtained as follows. On the first image showing an increased T_1 value (>390 ms) we selected the T_1 value from an area anatomically remote from the site of infarction to control for and give information about the variability of T_1 measurements with our system. T_1 values for this selected non-affected region were noted for subsequent examinations.

The data were analysed in both a cross sectional and longitudinal manner. In the cross sectional analysis the maximum T_1 for all patients at each time period after infarction is presented as a mean and 1 SD. The variation in T_1 with time since infarction was studied by fitting a gamma variate curve to the mean maximum T_1 values at each time period and calculating the regression coefficient. The maximum T_1 at day 1–3 was compared with the value obtained from the non-affected region on the same scan by means of a paired Student's *t* test. Linear regression analysis was used to correlate the maximum T_1 values and the number of areas of increased T_1 with left ventricular ejection fraction and peak creatine kinase activity.

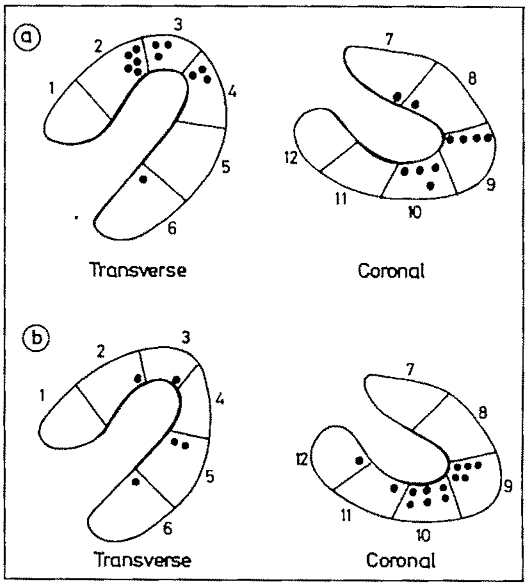

Fig 1 *(a) Regions of myocardium with greatest T_1 value in patients with anterior infarction. Each dot represents the region with the maximum value for a single patient. (b) Regions of myocardium with greatest T_1 value in patients with inferior infarction.*

Longitudinal analysis of the data was performed by noting the change in T_1 at each study interval.

Results

T_1 VALUES IN THE NON-AFFECTED AREA

For the group as a whole the mean T_1 of the non-affected myocardium at day 1–3 was 320 (19) ms. There was no significant difference in the measured T_1 at any time in the non-affected region, the highest mean value being 326 (18) ms at one month. The range of T_1 values in the 41 patients over all time periods was 274–382 ms, confirming our previous observation that a cut off of 390 ms differentiates between normal and infarcted myocardium.[7]

T_1 VALUES IN THE AFFECTED AREA

Maximum T_1 values

Table 2 shows the results for each patient at the six times after infarction. Maximum T_1 values always occurred in an anatomical position consistent with the electrocardiographic changes (fig 1a and b). But the highest T_1 was not always seen in the same region on serial imaging.

Cross sectional analysis of the data (fig 2) showed that at day 1–3 T_1 was significantly higher in the infarct region than in the non-affected area

Table 2 *Patient details, maximum creatine kinase (CK) and T1 values at intervals shown*

Patient No	*Age*	*Site of infarct*	*Successful thrombolysis*	*Max CK*	T_1 *maximum*					
					Day 1–3	*Day 4–7*	*Day 8–14*	*1 mnth*	*3 mnth*	*6 mnth*
1	39	Lateral	Yes	717	480	—	476	462	397	399
2	45	Inferior	Yes	1261	—	435	443	374	—	—
3	64	Inferior	No	1395	—	—	—	476	427	—
4	58	Inferior	No	1230	415	404	447	454	410	378
5	70	Anterior	Yes	1169	371	—	539	—	—	348
6	55	Anterior	Yes	2624	—	475	—	452	400	389
7	37	Anterior	Yes	3117	366	—	409	399	377	—
8	49	Inferior	No	1529	—	389	468	439	322	356
9	56	Inferior	Yes	2076	—	—	—	—	430	353
10	54	Anterior	Yes	4578	428	507	455	451	408	366
11	60	Anterior	Yes	789	414	472	483	402	—	364
12	46	Inferior	Yes	2361	—	400	379	—	—	344
13	60	Inferior	Yes	1030	435	—	—	—	—	356
14	67	Inferior	Yes	799	378	386	—	—	357	—
15	57	Anterior	Yes	513	—	452	—	—	—	—
16	48	Anterior	Yes	2743	—	—	—	391	—	361
17	53	Anterior	Yes	4565	414	402	420	453	478	372
18	61	Anterior	Yes	3602	—	—	474	—	—	—
19	57	Inferior	No	1301	392	—	397	470	363	344
20	56	Inferior	No	3156	410	—	—	—	—	—
21	73	Anterior	No	699	431	469	468	—	346	385
22	49	Anterior	No	2215	—	—	400	358	358	—
23	42	Lateral	Yes	3719	441	439	438	425	392	—
24	33	Anterior	Yes	1736	442	502	—	405	—	412
25	57	Anterior	Yes	247	429	387	—	—	—	—
26	62	Anterior	Yes	881	—	397	—	—	371	359
27	40	Inferior	No	—	—	460	390	—	360	350
28	42	Anterior	Yes	1652	—	—	396	—	423	338
29	56	Anterior	No	3025	—	—	—	—	—	412
30	63	Inferior	Yes	814	—	—	—	—	364	343
31	52	Inferior	Yes	1286	—	—	—	—	393	347
32	58	Anterior	No	2869	426	—	—	—	—	—
33	61	Anterior	Yes	1701	—	—	408	—	—	—
34	58	Anterior	Yes	4372	435	396	—	424	438	376
35	58	Anterior	Yes	—	—	—	—	—	—	374
36	58	Anterior	Yes	203	402	428	372	429	—	—
37	61	Inferior	Yes	1303	390	365	393	390	346	—
38	44	Anterior	No	2138	404	465	456	427	472	—
39	58	Inferior	No	1216	374	394	469	387	383	—
40	73	Inferior	No	1890	443	—	442	410	355	—
41	62	Anterior	Yes	2723	371	441	443	384	392	—

($p < 0.0001$). T_1 continued to rise, reaching a peak at day 8–14 before falling gradually towards normal. Fig 3a–d shows images from one patient at increasing intervals after infarction. The gamma variate curve fitted to the change in peak T_1 gave a significant correlation coefficient ($r = 0.95$, $p < 0.001$).

The results of longitudinal analysis, which combined the changes in individual patients, supported the trend shown in fig 2.

Area of raised T_1 (fig 4)

In this study 38 of the 41 patients had a maximum T_1 of >390 ms. Of the 23 patients who had their first scan between the first and third day after the onset of infarction, five had no regions of interest with a T_1 above 389 ms. In four of these, however, the T_1 subsequently rose to more than 390 ms by the time of the second scan on day 4–7. Only one patient did not demonstrate a T_1 value above 390 ms on at least one scan; the maximum T_1 value in this patient was 386 ms.

The number of areas with significantly increased T_1 varied greatly both between patients and at different times. The same general pattern to that of the peak T_1 values was found. By six months only two patients had any areas of T_1 >390 ms.

COMPARISON OF REPERFUSED AND NON-REPERFUSED GROUPS

The maximum T_1 and number of areas of increased T_1 (above 390 ms) were not significantly different between the two groups at any time period. Neither was there any significant difference in T_1 values between those patients in the reperfused group who were treated early (within two hours) and those who were treated later, although there was a trend towards a more rapid fall in the number of areas of raised T_1 in the group treated early.

IDENTIFICATION OF INFARCT SITE

For inferior infarcts the maximum T_1 was most commonly seen on the coronal image (fig 1a) but

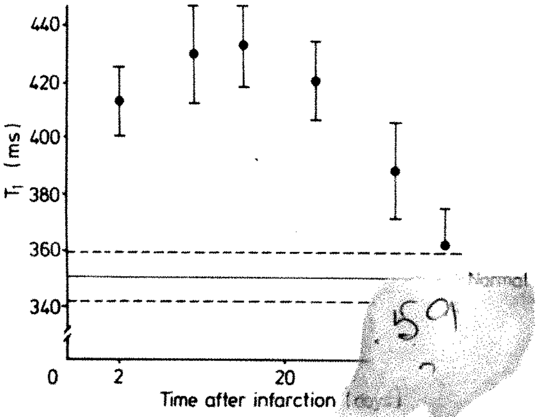

Fig 2 *Mean maximum T_1 values (2 SE) after myocardial infarction. Values were greater than the normal mean maximum T_1 (SE) at first imaging (day 1–3) and tended to increase until the third imaging sequence (day 8–14); values only returned to the mean maximum T_1 values seen in normal subjects six months after infarction.*

maximum T_1 values were more commonly seen on the transverse views when there was an anterior infarct (fig 1b).

CORRELATION OF T_1 WITH OTHER MEASURED VARIABLES

Creatine kinase

Because inferior infarcts tended to have a smaller peak activity of creatine kinase (1471 (581) *vs* 2162 (428) U/l) and left ventricular function was better preserved (52 (7)% *vs* 32 (11)%), they were first considered separately from anterior infarcts. There was no significant difference in maximum T_1 values between anterior and inferior infarction, however. There was a correlation ($r = 0.59$, $p < 0.01$) between the peak activity of creatine kinase and the maximum T_1 found at three months in the combined groups.

Left ventricular ejection fraction

There was a correlation between ejection fraction and peak T_1 values at one month ($r = -0.57$, $p < 0.05$). The number of areas of increased T_1 (> 390 ms) correlated with ejection fraction at 4–7 days ($r = -0.63$, $p < 0.01$), 8–14 days ($r = -0.53$, $p < 0.05$), and at one month ($r = -0.6$, $p < 0.02$).

Discussion

After myocardial infarction T_1 rises in the area of infarction in almost all patients. There is no significant change in T_1 in the unaffected myocardium. This confirms reports of in vitro[2 3] and in vivo[5 6] experimental studies and those in human infarction.[7 8] The changes may not appear or be appreciable before four days after the onset of infarction, and they reach a peak by the end of the first week. While it is likely that there was some increase in T_1 during the early stages of infarction in all our patients, the magnitude of this increase was not sufficient to permit reliable identification of abnormal myocardium in every case. The values in the five patients who did not have a T_1 > 390 ms on their initial scan ranged from 366 to 378 ms compared with a mean 320 (9) ms in the normal myocardium and they were within our previously reported range for normal myocardium.

Our finding that maximum T_1 values occurred at about two weeks was unexpected. The reported close correlation between T_1 and water content[2] suggests that a more uniform and rapid increase in T_1 would be expected, because myocardial interstitial oedema and mitochondrial swelling occur early after the onset of infarction.[1 3] The dissociation between the timing of the peak T_1 and the expected peak of myocardial oedema formation may partly be explained by the fact that T_1 depends not simply on the total myocardial water content but also on the binding or interaction of water with biological macromolecules.[1]

The difference between our findings and previous in vitro studies of early changes in T_1 is likely to reflect the major differences between ischaemic human myocardium and excised heart muscle. Not only will the quantity of blood in the intramyocardial vessels differ, as does the coronary anatomy, but in addition there are differences in the state of binding of water within cells. In living systems metabolic processes continuously produce water and its biological state is regulated by cellular processes. That such differences affect T_1 has been demonstrated by comparative in vivo and in vitro T_1 measurements in rabbits.[14]

Our results accord with the in vivo experimental work of Pflugfelder *et al* who studied the serial changes in relaxation parameters and signal intensity in eight dogs after myocardial infarction.[8] In one animal the increase in signal intensity was only seen 4–6 days after infarction. The timing of peak signal intensity was dependent on the pulse sequence used but occurred between the fourth and thirteenth day. Furthermore, these workers frequently found an area of increased signal intensity on day 20 (the final image) and they commented that the affected area seemed to get smaller. Similarly in our study T_1 values remained raised at one month and even in some patients at three and occasionally six months, but the number of areas of increased T_1 fell more rapidly.

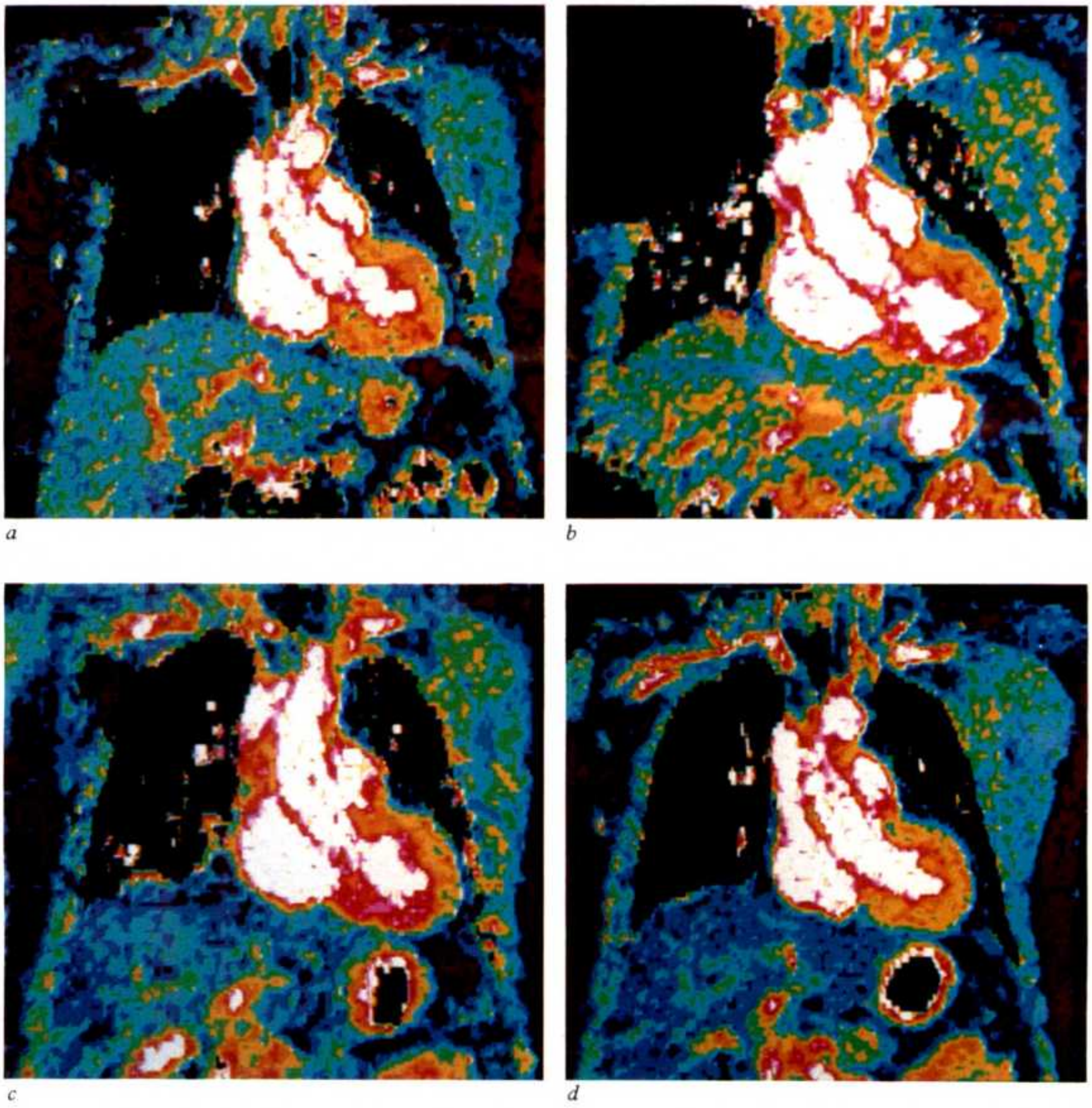

Fig 3 *Sequential coronal images in a patient with inferior infarction: (a) 3 days, (b) 14 days, (c) 1 month, and (d) 3 months after infarction.*

The presence of T_1 prolongation for up to three months confirms that factors other than myocardial oedema are responsible. The classic histological findings[15 16] after myocardial infarction indicate that neutrophils appear after about six hours and increase rapidly after 24 hours, reaching a peak between the third and fifth day.[15 17] Thereafter the number of large mononuclear macrophages increases, reaching a maximum at six weeks and subsequently declining. Other cellular infiltrates also occur, as does proliferation of capillaries which reaches a peak between 3–6 weeks. The histological changes may vary in the same patient at various times.[17] These cellular changes may influence magnetic resonance variables but, as yet, precise histological correlations are not possible. The possibility that T_1 and T_2 changes may provide a method of obtaining in vivo information about pathogenesis is exciting and has received some support from the recent finding that T_2 correlates with the histological severity of rejection in

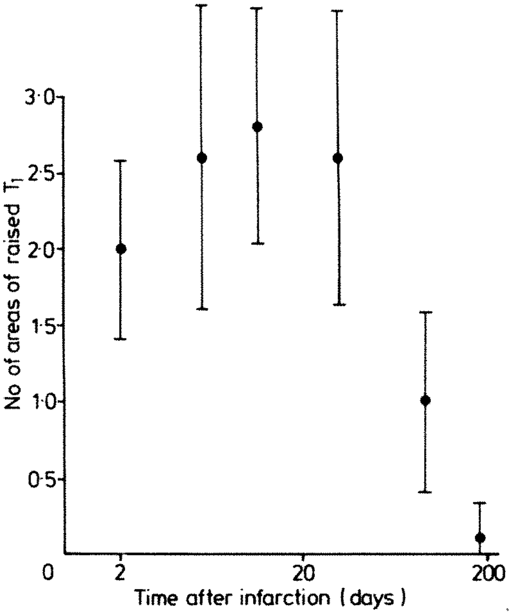

Fig 4 *Number of areas (mean (1 SE)) of myocardium with raised T_1 (> 390 ms) after myocardial infarction. The changes with time follow the same pattern as the changes in maximum T_1.*

heterotopic cardiac transplantation in dogs.[18]

Some studies have suggested that T_2 is better than T_1 for the identification of infarcted tissue, but this may reflect different imaging sequences where the pulse sequence combination used was more appropriate for T_2 measurements than for T_1. Spin echo sequences with a short time to recovery do not contain as much T_1 weighting as an inversion-recovery sequence. In addition, variation in a patient's RR interval can influence time to recovery in the spin echo sequence causing a variable T_1 weighting and, as a consequence, error in the T_1 value. The constant time for inversion used in our technique, coupled with a non-slice selective efficient inverting pulse, minimises the error in T_1 caused by variation in the RR interval.[12]

Ratner *et al* measured endocardial and epicardial T_1 and T_2 and correlates these variables with perfusion measured after 30 and 60 minutes of coronary occlusion.[19] They suggested that the magnitude of change in T_1 and T_2 correlates with the extent of the ischaemic insult. The magnitude of the ischaemic insult is dependent not only on the duration of vessel occlusion but also on vessel size, collateral flow, and the rate of oxygen consumption which all modify the response and determine the infarct size. In this clinical study our means of assessing infarct size were limited. We used the peak creatine kinase activity as a crude assessment of infarct size. There was a correlation with maximum T_1, but only at one month. Thus the maximum level of T_1 seems to correlate poorly with infarct size in clinical practice. Because the kinetics of creatine kinase release are altered by reperfusion we also measured left ventricular ejection fraction at 8–10 days. All patients included in this analysis presented with a first infarct and so the reduction in left ventricular function provides some information about infarct size. The number of areas of increased T_1 did correlate with the ejection fraction at 4–7 days, 8–14 days, and at one month. No correlation was expected at day 1–3 or at three and six months because some patients did not develop changes until after the third day and by three months the area of increased T_1 was considerably reduced. This correlation presumably reflects the amount of myocardium affected by the ischaemic event. Thus the extent of the area with abnormal T_1 values seems a better guide to infarct size than the magnitude of changes in T_1. When this study was undertaken we were unable to perform multiple slice acquisitions but with this capability a precise determination of the volume of infarcted tissue should be possible.

Studies of changes in T_1 in dogs after coronary occlusion and reperfusion have suggested that T_1 is further prolonged by reperfusion,[20] and an increase in cellular swelling after reperfusion has been reported.[13] None the less, we found no significant difference in maximum T_1 between our reperfused and non-reperfused patients. This may reflect a balance between beneficial and harmful[21] effects of reperfusion; however, further analysis of our data in which those given early and late thrombolytic treatment were compared gives no evidence of this. Because time to reperfusion is critically important[22] to the effect of reperfusion, it might be expected that the T_1 values would be different in these groups. There was no significant difference in maximum T_1 or the number of areas showing raised T_1 between those treated within two hours and those treated more than two hours after the onset of symptoms. We noted a trend towards a more rapid fall in the number of areas with a raised T_1 in those treated early. The small numbers in these subgroups and the heterogeneity of the patients (in terms of the vessel affected, the position of the lesion, rate of reperfusion, extent of residual stenosis, collateral flow, disease of other vessels and therefore of infarct size and degree of continuing ischaemia) may be masking real differences.

The factors which produce these alterations in T_1 are complex and as yet we do not know whether changes in T_1 values reflect specific histological findings. If the demonstrated changes reflect healing then alterations in T_1 may provide an important method for studying a neglected area in our understanding of myocardial infarction.

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Vasculitis complicating treatment with intravenous anisoylated plasminogen streptokinase activator complex in acute myocardial infarction

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SUMMARY Vasculitis developed in six of 253 patients treated with intravenous anisoylated plasminogen streptokinase activator complex (APSAC) after acute myocardial infarction. All patients recovered spontaneously with no evidence of renal impairment and no long term sequelae.

Although leucocytoclastic vasculitis and serum sickness have been reported after streptokinase treatment, such allergic reactions have not been described as a complication of other thrombolytic agents.

Anisoylated plasminogen streptokinase activator complex (APSAC) is a thrombolytic agent offering potential advantages that include ease of administration by intravenous injection over a few minutes.

The common unwanted effects of a related thrombolytic compound, streptokinase, include haemorrhage, fever, and an immediate allergic reaction.[1] Serum sickness[2-5] and crescentic glomerulonephritis[6] have also been described after streptokinase treatment, and in each case the patient had a purpuric rash. A further two papers describe non-specific rashes caused by streptokinase.[1-7]

We report the development of vasculitis in six of 253 patients treated with anisoylated plasminogen streptokinase activator complex after acute myocardial infarction.

Patients and results

In Brighton, up to June 1987, 253 patients presenting with suspected acute myocardial infarction had been treated with anisoylated plasminogen streptokinase activator complex (APSAC); all were treated within four hours of the onset of major symptoms. Each patient was given 30 units of anisoylated plasminogen streptokinase activator complex intravenously over four minutes together with conventional treatment with opiate analgesia, an antiemetic, and intravenous heparin.

In six patients (five male, one female) a purpuric rash developed 7–15 days after the administration of anisoylated plasminogen streptokinase activator complex. In each case there was purpura, particularly of the extensor surfaces of the legs. In two patients the rash also affected the extensor surfaces of their arms. The lesions varied from areas of purpura (3–7 mm in diameter) to necrotic vesicles (figure). The rash began to resolve after 2–5 days and had completely disappeared after three weeks. The table gives further details of the patients.

Five of the six patients developed arthralgia with swelling around their ankles as well as the rash. Of these, three had abdominal distension with colicky abdominal pain and diarrhoea. One patient with abdominal symptoms had melaena; endoscopy showed that the gastric mucosa was purpuric. These abdominal symptoms had a similar time course to the rash. No patient had clinical evidence of progressive renal impairment, although urinalysis showed mild proteinuria and haematuria in two patients.

No fall in haemoglobin concentration was detected, even in the patient who had melaena. Similarly, the platelet counts in each patient remained

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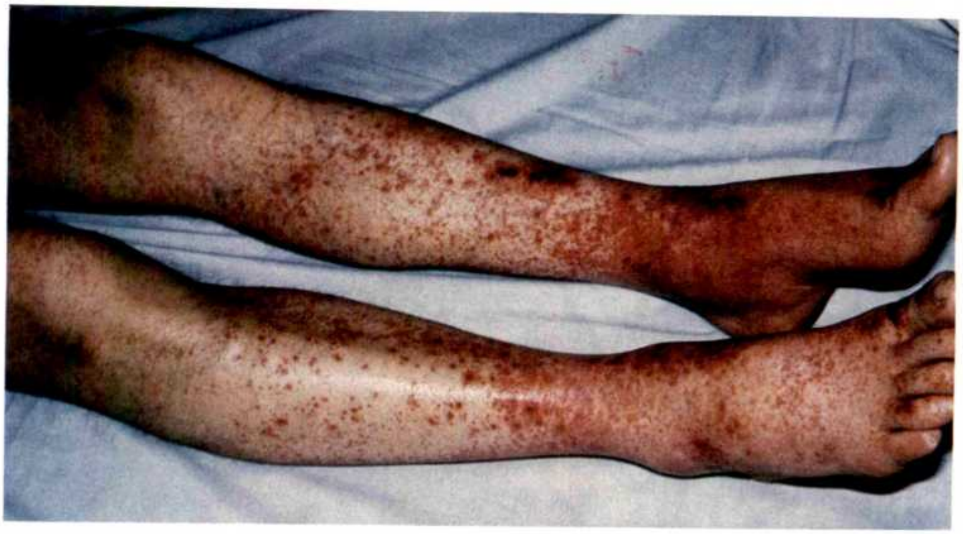

Figure *Allergic vasculitis of the legs.*

within the reference range. The plasma concentration of urea increased in the two patients with proteinuria and haematuria, from 6·7 to 10·1 mmol/l in one and from 5·2 to 23·5 mmol/l in the other (the patient with melaena), but the plasma concentration of creatinine did not exceed the upper limit of the reference range in either. During their hospital stay serum immunoelectrophoresis remained normal and antinuclear factors were negative in all six patients, but two patients had a positive rheumatoid factor. Skin biopsies were performed in two patients and showed lymphocytic vasculitis. Renal biopsies were not performed as all patients had a benign course.

Discussion

Drug induced vasculitis is a condition characterised clinically by a purpuric skin eruption that develops usually about 10 to 14 days after exposure to the drug.[8] Characteristically the rash affects the extensor surfaces of the arms or legs and resolves within three weeks of its onset.[8] Associated symptoms can include abdominal pain, arthralgia, gastrointestinal bleeding, and haematuria, suggesting serum sickness disease.[8] All six of our patients had a purpuric rash in the characteristic distribution, and five had associated symptoms. From a clinical point of view, therefore, the findings in these patients are suggestive of a vasculitis caused by the administration of anisoylated plasminogen streptokinase activator complex.

On skin biopsy, the features usually seen in patients with purpuric vasculitis are a neutrophil rich perivascular infiltrate, red cell extravasation, fibrinoid deposits in or around the blood vessel wall, and fragmentation of neutrophils (leucocytoclasia).[9] The biopsy specimens from our patients showed minimal leucocytoclasia, predominantly mononuclear cell infiltration around dermal vessels, virtu-

Table *Patient details*

			Myocardial infarction			*Rash*			*Associated symptoms*		
Patient	*Age*	*Sex*	*Site*	*AST max (0–41)* (U/l)*	*LDH max (120–360)* (U/l)*	*Site*	*Size (mm)*	*Onset (days)*	*Arthropathy*	*GI*	*Renal*
1	57	M	Inf	457	733	Legs	3–5	9	+	+	–
2	64	M	Ant	431	553	Legs	5	10	–	–	–
3	60	M	LBBB	85	489	Legs/arms	3–7	8	+	+	+
4	61	M	Ant	314	1739	Legs/arms	3–5	15	+	+	+
5	62	M	Inf	100	643	Legs	5	7	+	–	–
6	73	F	Ant	121	471	Legs	5–7	11	+	–	–

Ant, anterior myocardial infarction; AST, aspartate transaminase; GI, gastrointestinal; Inf, inferior myocardial infarction; LBBB, left bundle branch block; LDH, lactate dehydrogenase.
*Normal range.

ally no red cell extravasation, and no fibrinoid deposits. The biopsy specimens were taken just before the rash began to resolve in both cases. This may explain the absence of characteristic histological features.[9]

A large number of drugs have been reported to precipitate vasculitis. Sulphonamides, penicillins, and aspirin are prime offenders, but many high molecular weight drugs may act as antigenic sources.[8] Two patients had been prescribed thiazide diuretics before the onset of their reaction, but the four other patients had not received any medication before admission. An alternative cause for the rash may be heparin treatment, which had been given to all six patients. Heparin has been associated with hypersensitivity reactions after intravenous administration, but these have been of the immediate type.[8] Heparin is used routinely on our unit and we have never seen this type of rash before, although localised purpura at the injection sites has been seen after subcutaneous heparin.

The treatment of allergic vasculitis, usually a benign disorder, is largely empirical. The main factor determining prognosis is the degree to which the kidneys are affected, although gastrointestinal infarction and pulmonary involvement may occasionally lead to death.[8] Patients with multisystem involvement are often treated with corticosteroids, but evidence is lacking to show that such treatment alters the course of the illness.[8]

Awareness of this late complication of treatment with anisoylated plasminogen streptokinase activator complex is important for those treating acute myocardial infarction with this agent. The distinction must be drawn, however, between the long term benefit of myocardial salvage and the small risk of a transient allergic reaction that seems on present evidence to be benign.

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Digital subtraction contrast echocardiography: a new method for the evaluation of regional myocardial perfusion

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SUMMARY The potential of contrast enhanced digital subtraction echocardiography to demonstrate and quantitate myocardial perfusion was evaluated in 36 patients undergoing routine coronary arteriography or angioplasty. In 24 technically successful studies, multiple cross sectional echocardiographic images, obtained before and after intracoronary (sonicated contrast) injection, were stored by high speed, real time data transfer to an on line minicomputer. Subsequent digital subtraction processing of the stored image data provided composite images in which the distribution of myocardial perfusion was easily seen. Quantitative analysis of peak enhanced myocardial grey level and washout half time successfully differentiated between myocardial segments in which angiography had suggested normal, reduced, and grossly impaired or absent perfusion.

The results suggest that this new method of digital image capture and quantitative processing has substantial advantages over previous off line qualitative techniques. It is likely to be of considerable value for routine coronary arteriography, angioplasty, and coronary thrombolysis.

Myocardial contrast echocardiography is now recognised as a convenient and safe method of obtaining information about regional myocardial perfusion.[1 2] Contrast enhancement of images of the myocardium is almost certainly due to an acoustic impedance mismatch between the myocardial tissue and the gaseous bubbles generated within the contrast medium.[3]

Over the past few years several improvements in the technique have increased its applicability. The most important of these has been a change from hand agitated to sonicated contrast medium.[3] Renografin-76, which is widely used for coronary angiography, has been used as an echocontrast medium. Preparation of contrast by hand agitation has an adverse effect upon the myocardium because it produces large bubbles (about 20 μm in diameter)[4 5] These seem to cause capillary occlusion. Sonication of the contrast medium creates much smaller and more reproducible bubbles with diameters of approximately 10 μm. These have capillary transit times similar to red blood cells.[6] No deleterious effects upon the myocardium have been described with this new method of preparation.[2]

In this study sonicated Omnipaque-350 (iohexol) was used as the contrast agent. This is a non-ionic *x* ray contrast medium which seems to be more suitable for myocardial echocardiography than Renografin-76. Unlike Renografin it has a limited hyperaemic response and the microbubbles are more stable. These are highly desirable attributes in an ultrasound contrast agent, especially for the measurement of myocardial washout times.[7]

Subjective evaluation of the distribution of myocardial contrast has proved possible in many patients.[8] The technique has been limited, however, by several technical factors which reduce the quality and usefulness of the contrast images. These include a dependence on the ultrasound equipment instrument settings, image degradation by the output and video recorder circuitry (with inadequate bandwidth), and difficulties caused by high

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background grey levels in the myocardium. Attempts to quantitate perfusion by measuring grey level variables have met with limited success in humans,[9] presumably for the same reasons.

Use of the method we describe attempts to circumvent many of these problems with a stable sonicated contrast medium and, more importantly, by acquisition of raw digital scan line data from within the scanner. Subsequent subtraction processing of the image data within an on line computer was performed to try to facilitate quantitative measurement of myocardial perfusion and also to produce an image in which the spatial distribution of perfusion is easily seen.

Patients and methods

PATIENTS

Thirty six patients undergoing coronary arteriography were recruited. Of these, eight were rejected because technically adequate parasternal echocardiographic images could not be obtained while they were supine. The remaining 28 (10 women and 18 men) patients were aged from 38 to 76 years (mean 56). Four of these patients were undergoing angioplasty procedures—two to the left anterior descending coronary artery, one to the right coronary artery, and one to a left circumflex graft.

A total of 110 intracoronary contrast injections were made in these patients. Thirty nine (35%) of the image sequences collected from these injections were considered to be inadequate, which resulted in the total exclusion of data from a further four patients. This was either because of inappropriate contrast administration (11 sequences), faulty computer data collection (six sequences) or, most commonly, frame misalignment (22 sequences). For successful subtraction processing it is essential that all the images are lined up exactly, with no spatial movement of the endocardial borders between frames. Improvements in the technique of contrast administration and additional computer software to correct for frame misalignment now mean that very few image sequences have to be rejected.

The coronary angiograms in those 24 patients in whom the 71 successful injections were made were analysed by two independent observers. They identified 30 myocardial segments or coronary territories where, unequivocally, one would expect normal perfusion. The coronary arteries supplying those segments were entirely without lesions and, in addition, the segments showed normal wall motion and systolic thickening on the echocardiogram.

A further 36 segments or territories were selected where the coronary supply was abnormal, and reduced perfusion would be expected. In these cases the coronary lesions were proximal and caused between 70% and 90% stenosis or >90% stenosis with evidence of some limited collateral supply.

Finally, 28 segments were identified in which no perfusion or grossly impaired perfusion would be expected. Again the coronary lesions had to be proximal and causing at least 95% stenosis. There was no collateral filling and wall motion and thickening were abnormal in these segments on the echocardiogram.

Those echo segments that corresponded to the coronary territories identified above were analysed by subtraction processing of the contrast data.

CONTRAST AGENT

Coronary angiography or angioplasty was performed from the femoral approach in all cases. Most patients had two injections of sonicated contrast into the left coronary artery and two into the right coronary artery or coronary graft. Data were acquired in two different echo scan planes (as described later). This added a maximum of five minutes to the standard catheterisation procedure.

The contrast medium was 3 ml of sonicated Omnipaque-350 (iohexol) *x* ray contrast medium. This is a non-ionic medium with a concentration of 350 mg of iodine per millilitre and a viscosity of 10·6 mPa.s at 37°C. During the contrast injections there were no important changes in either blood pressure or electrocardiographic configuration.

Sonication was performed with a Vibracell sonicator, with a ½" horn and an energy of 250 W for 20 seconds. The technique and method of microbubble formation by sonication have been described elsewhere.[3] Samples of sonicated Omnipaque contrast medium were examined by light microscopy and this showed a mean (SD) bubble size of 9·2 (3·8 μm). For comparison, sonicated Renografin-76 was also examined and found to contain bubbles of a similar mean (SD) size (10·3 (4·5) μm). The concentration of bubbles in Omnipaque seemed to be less than that in the Renografin; however, the bubbles were much more stable with approximately 90% persisting at three minutes. These differences between the two contrast agents have been confirmed by in vitro experimentation. This demonstrated that Renografin-76 generates higher initial ultrasound backscatter intensity which decays very quickly to 50% within two minutes. Measurement of myocardial washout time and use of the same prepared sample of contrast agent for multiple injections demand an agent with stable microbubbles.

ECHOCARDIOGRAPHY

The echo contrast recording for each coronary artery was performed at the end of the normal sequence of angiographic image planes. In most cases, both mitral valve and papillary muscle parasternal short axis frame sequences were collected for injections into the left and right coronary arteries. During the procedure the transducer was kept stationary on the chest wall and the patient was asked to limit respiration. This reduced movement of the heart relative to the image plane. The echo images were gated to the R wave of the electrocardiogram so that only the end diastolic frames were collected. A total of approximately 27 sequential frames was transmitted to the computer with contrast being injected after the fourth frame (fig 1).

A 3·5 MHz medium focus echo transducer was used in all cases. The ultrasound instrument was a Hewlett-Packard 77020 phased array scanner that was specially modified to incorporate a high speed, bidirectional data link allowing on line, real time transmission of image scan line data to an HP 1000 minicomputer in an adjoining room. The computer was equipped with 2 Mbytes of random access memory, 45 Mbytes of hard disc memory, full floating point processing, and a standard range of output peripherals.

A computer terminal (to the HP 1000) was also positioned in the catheter laboratory and this was used to control the transmission of data between the echo equipment and the computer. With this terminal it was possible to select any portion of the images for transmission to the computer. By only storing the relevant part of the images (that is just the short axis of the left ventricle and no right ventricular or extracardiac structures) considerable computer memory was saved. This memory saving allowed us to capture more frames.

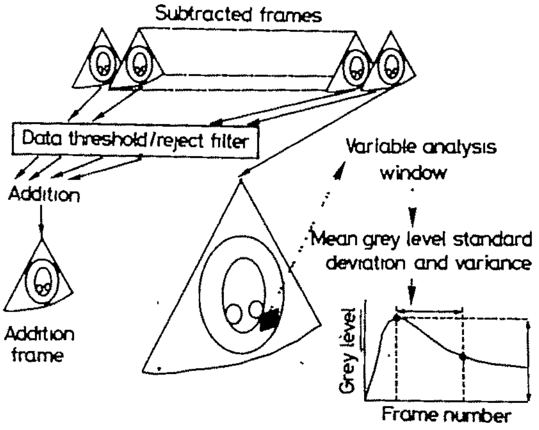

Fig 2 *Diagram showing how the subtracted frames are further processed in two ways. A variable analysis window is used to calculate mean grey level, standard deviation, and variance for every frame in multiple positions on the image. The mean grey level is plotted (after smoothing) and the peak level and time (in beats) to half peak value is computed. After subtraction the frames can be added together (after passing through a low level reject filter) to produce a composite addition frame that clearly shows the distribution of perfusion.*

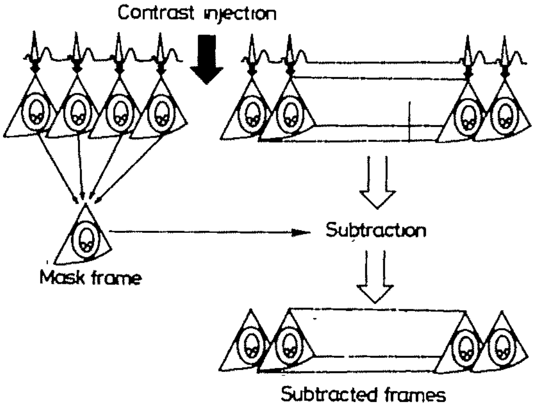

Fig 1 *Diagram showing how multiple sequential R-wave gated frames are transmitted to the computer. Contrast was injected after the fourth frame. The pre-injection frames are averaged to produce a mask which is subtracted from the post-injection frames. The resulting sequence of subtracted frames shows only those areas where there is enhancement of grey level contrast in the myocardium.*

DATA PROCESSING AND ANALYSIS

Figures 1 and 2 show how the captured frames were subsequently processed in the computer system. At any time the entire image sequence of processed or unprocessed frames could be reviewed by replaying through the scan converter in the ultrasound system. The alignment of all the images was checked before processing. Any sequences in which one or more of the frames had moved in relation to the others were discarded.

The four pre-injection frames were averaged to produce a mask frame. This was accomplished by calculating a mean grey level value representing each data point down every scan line for all four frames. The resultant pre-injection frame-averaged mask had a smoothed appearance with an expected reduction in random noise (figs 3 and 4).

Digital subtraction was then performed by subtracting the grey level values in the mask frame data points from the corresponding grey levels in all the post-injection frames. Any resultant negative

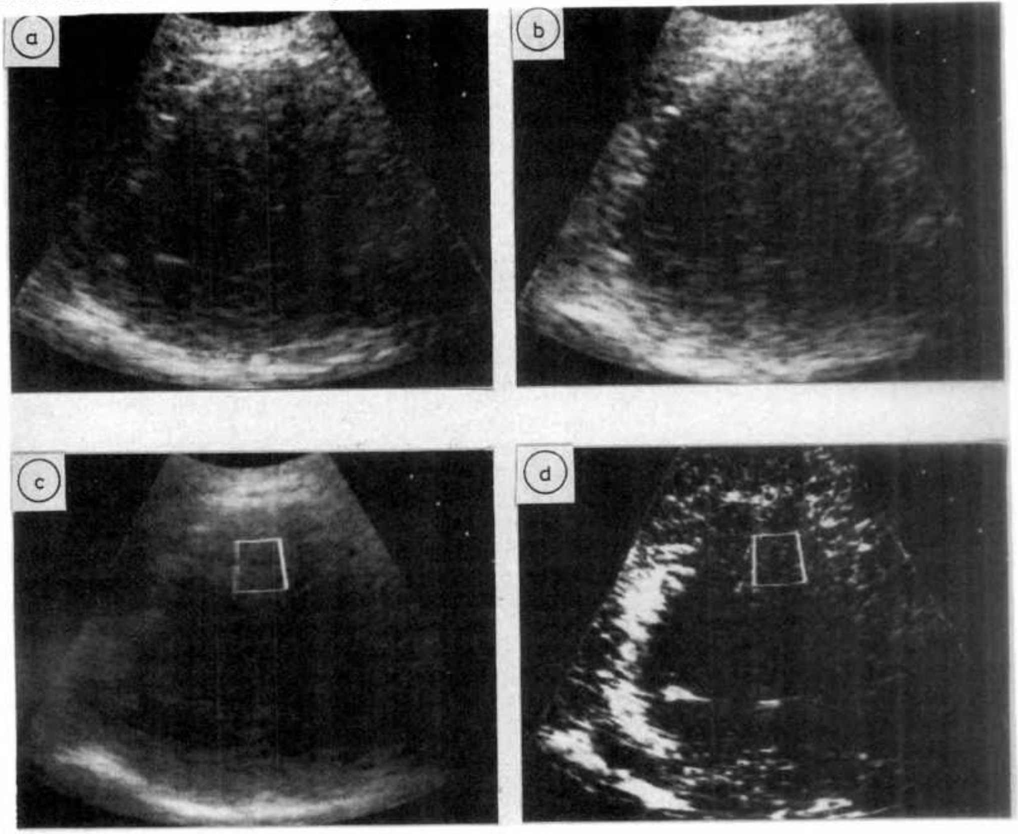

Fig 3 *Examples of parasternal short axis images obtained before (a and c) and after (b and d) injection of contrast into a normal right coronary artery. (a) and (b) are digitally captured unprocessed images that have not been degraded by video recording. (a) was obtained before the injection and (b) after injection at peak grey level enhancement. (c) is the pre-injection mask frame and (d) is the composite addition perfusion image which clearly shows perfusion in the territory of the right coronary artery. It is easier to evaluate perfusion from (d) than by assessing the differences between images (a) and (b). The variable analysis window is shown in (c) and (d).*

values were set to zero. The resulting series of subtracted frames showed only those areas in which the myocardial grey level was enhanced (by contrast) and this was virtually independent of instrument settings and background myocardial grey level.

To study the spatial distribution of myocardial perfusion, an additional image was created by adding the frames together after subtraction of the mask. Therefore, myocardial segments that were persistently enhanced throughout most of the subtracted sequence became very bright. Conversely, unperfused segments remained dark. To prevent low level noise signals being added together, any grey levels below a threshold value of 15 units were rejected before the frames were summed. This was the lowest threshold that would exclude random noise signals within the left ventricular cavity from the addition. We assumed that the same reject value would also prevent noise in unperfused segments from causing significant brightness when the frames were added together. This addition process produced a composite addition image with a bistable appearance—perfused areas were almost white and unperfused areas were dark (figs 3 and 4).

Previous myocardial contrast studies of experimental preparations have suggested that measurement of the kinetics of contrast enhancement may be used to evaluate perfusion.[10 11] A variable window for quantitative analysis that could be changed in size and position was used to facilitate similar measurements in our patients. The mean grey level,

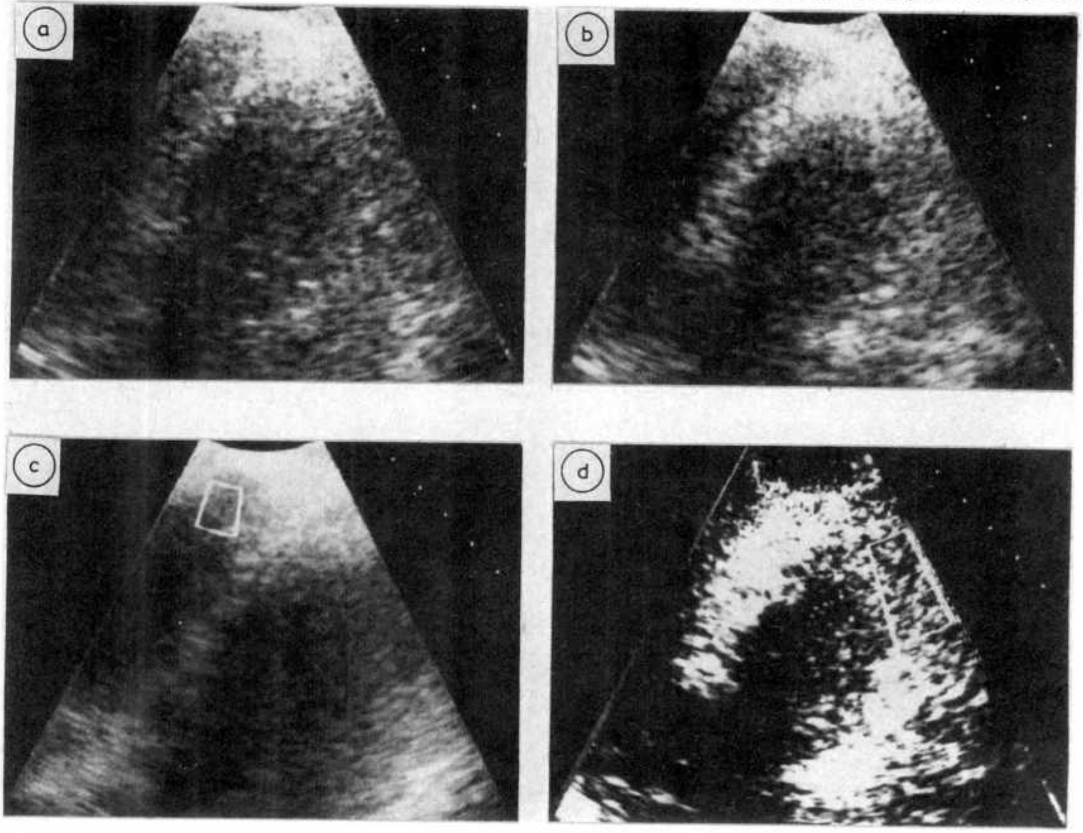

Fig 4 *The same sequence of images as shown in fig 3 before and after injection of contrast into the left coronary artery. Subjective determination of contrast enhancement is difficult because there is a low signal to noise ratio in the unprocessed images and the background myocardial grey level is high. The distribution of perfusion, however, is easily seen in the composite addition image (d). The quantitative variable analysis window is shown in (c) and (d).*

standard deviation, and variance for the data within the window was calculated by the computer for every frame. The mean grey level was plotted after data had been passed through a three point centre-weighted smoothing algorithm. This feature is shown in fig 2 and examples of the analysis window are seen in figs 3 and 4.

Myocardial regions, broadly identified on standard cross sectional imaging planes, can be correlated with the distribution of the normal epicardial coronary anatomy.[12 13] Figure 5 shows the expected distribution of perfusion zones for each coronary artery for the short axis imaging planes used in this study. To allow for variability in the exact distribution between patients, the quantitative analysis window was positioned in the centre of each region as shown. For measurements in the left anterior descending territory the window was positioned in the most anterior septal segment close to the junction of the anterior right ventricular free wall. Measurements of territory of the left circumflex coronary artery were made between the posterior lateral and medial papillary muscles and an equivalent geometric position was used at mitral valve level. Finally, the window was positioned at the junction of the posterior right ventricular free wall and the interventricular septum to measure perfusion by the right coronary artery.

We measured the peak (subtracted) grey level and the time taken (in terms of number of beats) for the peak to decay to half. This should represent the myocardial washout time of the contrast and be inversely related to myocardial perfusion. These data were calculated for all the segments in which angiography had suggested normal, reduced, and zero or grossly impaired perfusion.

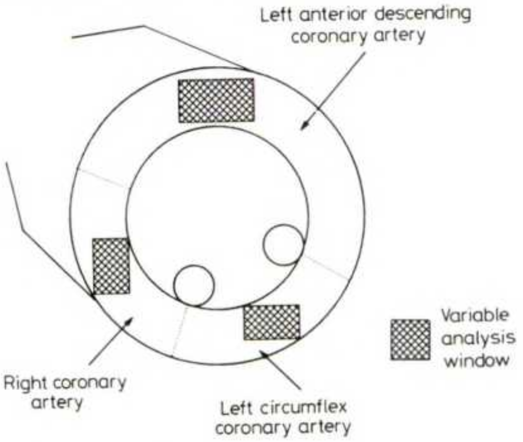
Left anterior descending coronary artery
Variable analysis window
Right coronary artery
Left circumflex coronary artery

Fig 5 *The normal perfusion zones of each coronary artery*[12 13] *in images obtained in the parasternal short axis plane. The position of the variable analysis window in the centre of each zone is shown.*

Results

Figures 3 and 4 are two typical examples of unprocessed and processed myocardial contrast images. The composite addition image in fig 3 shows normal right coronary perfusion extending high into the medial septum. The spatial distribution of perfusion is much more obvious in the composite image than in the unprocessed examples. Figure 4 shows the identical arrangement of images in a patient undergoing injection of contrast into the left coronary artery. Here the unprocessed images are quite "noisy" and there is a broad range of background baseline echo intensities which makes subjective determination of enhancement difficult. In the composite addition image, however, distribution of perfusion into the territories of left anterior descending and circumflex arteries is clearly seen.

Four of the patients whom we studied were undergoing angioplasty procedures. Figure 6 shows data taken from the anterior septal segment in one of these patients immediately before and after successful dilatation of a lesion of the proximal left anterior descending coronary artery. After the procedure the peak grey level was considerably increased and the washout half time was appreciably shortened, pointing to an increase in segmental myocardial perfusion.

Figure 7 shows the results of quantitative analysis of peak grey level and washout half time in those segments in which angiography showed normal, reduced, or no perfusion. There was a highly significant difference between the three groups in peak grey level, with mean values of 12·54 beats for the normal group, and 8·72 and 4·19 respectively for the groups with reduced perfusion and no perfusion.

The myocardial washout half time for the group of segments with no perfusion or grossly impaired perfusion is theoretically, and also in practice, virtually infinite. It has, therefore, been shown to extend beyond the scale of the graph in fig 7. Again, there was a highly significant difference between the washout time in the groups of segments, with mean values of 8·11 beats for the normal group and 15·48 for the group of segments with reduced perfusion.

Discussion

This study confirmed earlier reports that myocardial contrast echocardiography can be performed with ease and safety.[1 2] The methods we describe provide clear images of the perfusion beds of the coronary arteries. The technique also seems to be able to discriminate between different levels of regional myocardial perfusion in humans.

Experimental studies have shown an excellent correlation between the abnormal distribution of contrast in the myocardium and areas of infarction or severe ischaemia.[14 15] However, in humans the images are often technically inadequate especially in patients in whom this technique would be of particular value. If these images with low signal to noise ratio and a broad range of baseline echo intensities are further degraded by video recording, then subjective analysis of contrast enhancement is at best difficult and quantitative analysis is virtually impossible.

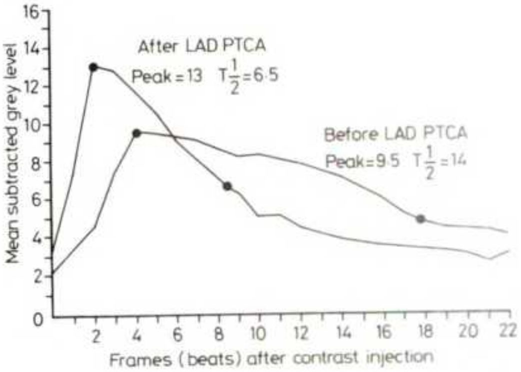

Fig 6 *Results of perfusion analysis in the territory of the left anterior descending coronary artery of a patient immediately before and after successful angioplasty of a proximal lesion. The peak grey level and washout half time values are given; they both indicate increased segmental perfusion.*

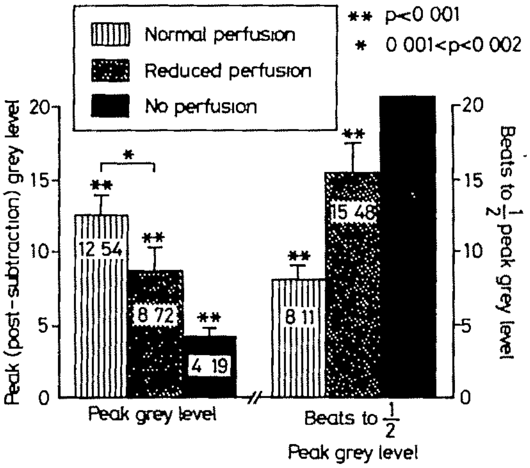

Fig 7 *Peak grey level and washout half times (and 95% confidence interval) for segments of presumed normal, reduced, and zero or grossly impaired perfusion. The differences in these two variables were significantly different for all the comparisons between the three groups. p was $< 0{\cdot}001$ except for differences in peak grey level between the normal and reduced perfusion groups where p was $< 0{\cdot}002$. The washout time for the group with no perfusion is infinite and has been shown extending beyond the scale of the graph.*

In the present study on line digital capture of the scan line echo data avoided these problems of image degradation. Subsequent digital subtraction processing seems to reduce the variable effects of instrument settings and facilitates study of the spatial distribution of perfusion, when a subjective approach would be difficult. The ability of digital subtraction angiography to provide high quality contrast enhanced radiographic images is now accepted. The techniques that were applied to echocardiography in this study are completely analogous. In addition, the computer processing of a complete sequence of echo contrast images is rapid enough to allow replay of the processed frames into the catheter laboratory during the same procedure.

The major technical problem with the technique seems to be that of frame misalignment. The creation of additional software that permits spatial translation of individual images has now largely circumvented this problem and together with improved techniques of contrast injection has considerably reduced the number of rejected image sequences.

The results of this study indicate that with digital subtraction, echocardiographic quantification of myocardial perfusion by analysis of the kinetics of myocardial contrast enhancement may be easier than has been previously suggested.[9] [11] There were, however, several factors that undoubtedly contributed to the highly significant differences in the grey level variables between the groups of myocardial segments in our patients. First of all, the segments were carefully selected, according to the previously described criteria, so that they clearly represented three very different levels of perfusion and any overlap between the segment types was unlikely. Secondly, the method has been improved by (*a*) the use of a non-hyperaemic contrast agent with greater bubble persistence; (*b*) direct on line digital capture of echo image data; (*c*) subtraction processing of the data to enhance differences in myocardial grey levels by removal of background signals; and (*d*) measurement of washout half time as beats rather than as time units. We feel that this last factor is important because coronary flow is largely proportional to heart rate and would undoubtedly influence contrast washout time. Therefore, there is a strong argument for correcting this measurement for heart rate if it has not been measured in terms of beats.

Further improvements in echo contrast media for human use can be expected soon. These will include purpose-made contrast agents containing microspheres that are very stable and hyperreflective to ultrasound. They can be made of albumin and seem to be capable of traversing the pulmonary capillary bed in sufficient quantities to facilitate opacification of the left heart and myocardium.[16] The ability to study myocardial contrast distribution after intravenous injections has obvious advantages.

The application of computer technology to the storage and processing of the raw ultrasound data from echo contrast images in a digital format makes the analysis of regional myocardial perfusion in humans a practical proposition. The technique has several advantages over other methods for delineating coronary perfusion beds: it has excellent spatial resolution, it can be repeated at short intervals, and it costs less than radioisotope methods. With the planned development of ultrasound imaging systems incorporating the methods described in this study, the technique will undoubtedly evolve, not only as an adjunct to routine coronary arteriography, but also as a direct means of assessing the effects of intervention.

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Evaluation of collateral blood flow by myocardial contrast enhanced echocardiography

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SUMMARY Contrast enhanced cross sectional echocardiography is a new method for the real-time evaluation of regional myocardial perfusion. Two patients with a history of anteroseptal myocardial infarction and echocardiographically detected septal dyskinesia were examined by this new method. The first patient had two severe stenoses of the left anterior descending coronary artery and normal echocontrast opacification of the interventricular septum caused by collaterals from the right coronary artery. The second patient had good patency of left anterior descending coronary artery and no septal opacification. Thus contrast enhanced cross sectional echocardiography can be used to assess the importance of collateral blood flow in the myocardium.

Contrast enhanced cross sectional echocardiography is a new method of assessing perfusion within the left ventricular myocardium.[1 2] In experimental myocardial infarction there was no echocontrast opacification of the necrotic area after reperfusion, whereas in the marginal viable areas echocontrast slowly reappeared.[2] The size of echocardiographically assessed perfusion defect after reperfusion of the epicardial coronary artery correlated with the anatomical infarct size. During the past two years the first reports on the use of contrast enhanced cross sectional echocardiography of the human myocardium have appeared.[3 4] The present two case reports show the potential of this method for the evaluation of preserved perfusion in dyskinetic myocardium (and so probably of myocardial viability) and for the visualisation of collateral blood flow.

Patients and methods

CASE 1

A 66 year old woman had an anteroseptal myocardial infarction with subsequent left bundle branch block in 1984. Since then she had had progressive angina pectoris (New York Heart Association class III) and mild intermittent congestive heart failure. She had a complete cardiological evaluation including coronary arteriography in October 1986. The examination showed a severe double stenosis >90% of the proximal left anterior descending coronary artery with clinically insignificant lesions (<50%) in left circumflex and right coronary arteries. There were collaterals from the right coronary artery to the distal left anterior descending coronary artery. A dilated and diffusely hypokinetic left ventricle with an ejection fraction of 15% was shown by left ventriculography. Myocardial contrast enhanced cross sectional echocardiography was performed immediately after coronary arteriography. Sonicated iopamidol (4 ml)[5] was injected into the left main coronary artery and an echocardiographic apical four chamber view was recorded. There was considerable opacification of the lateral wall but no opacification of the dyskinetic septum and akinetic apex. (In a group of eight patients with normal coronary arteriograms we found in the apical four chamber view that the septum and apex were supplied from the left coronary artery.) During the subsequent right coronary injection there was considerable contrast enhancement of the septum (fig 1). Computer analysis of the time-intensity curve of myocardial echocontrast showed a longer contrast disappearance rate in the mid-ventricular level of the septum than in the lateral wall.

CASE 2

The second patient, a 61 year old man, showed the opposite pattern. A transmural anteroseptal myo-

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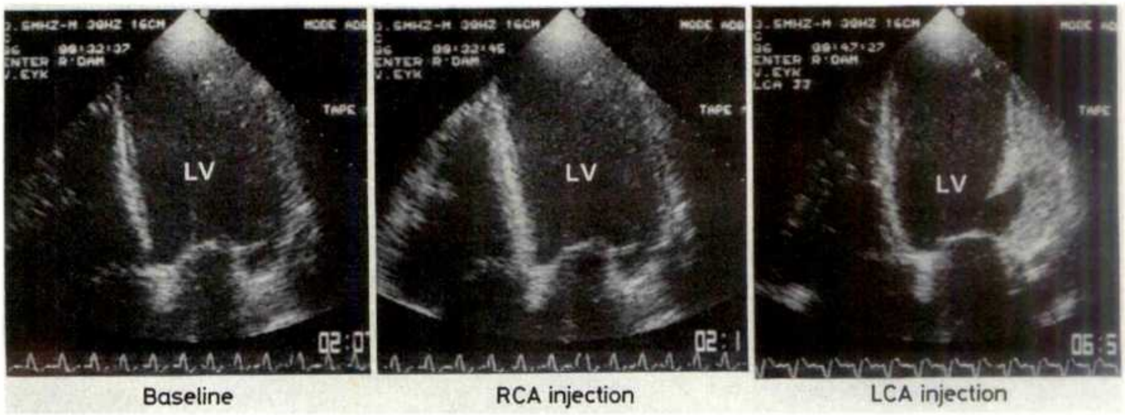

Fig 1 *Opacification of the interventricular septum by collaterals from the right coronary artery.* Left: *baseline apical four chamber view;* middle: *opacification of the whole septum after injection of the right coronary artery;* right: *opacification of the lateral wall and septal perfusion defect after injection of the left coronary artery. LCA, left coronary artery; RCA, right coronary artery; LV, left ventricle.*

cardial infarction in February 1986 was followed by a successful coronary angioplasty of a severe stenosis of the proximal left anterior descending coronary artery in April. Control coronary arteriography was performed in October 1986, followed by myocardial contrast enhanced cross sectional echocardiography. Only clinically unimportant lesions ($<50\%$) were seen in the coronary arteries, and there was good patency of the left anterior descending coronary artery. However, the branching of this artery was not visible. Left ventriculography showed apical dyskinesia with anteroseptal hypokinesia and ejection fraction of 26%. Cross sectional echocardiography showed septal akinesia. Contrast enhanced cross sectional echocardiography of the myocardium in the apical four chamber view showed contrast opacification of the normal lateral wall with no visible contrast in the apex and septum. Nor did injection of echocontrast into the right coronary artery show any septal opacification. Computer

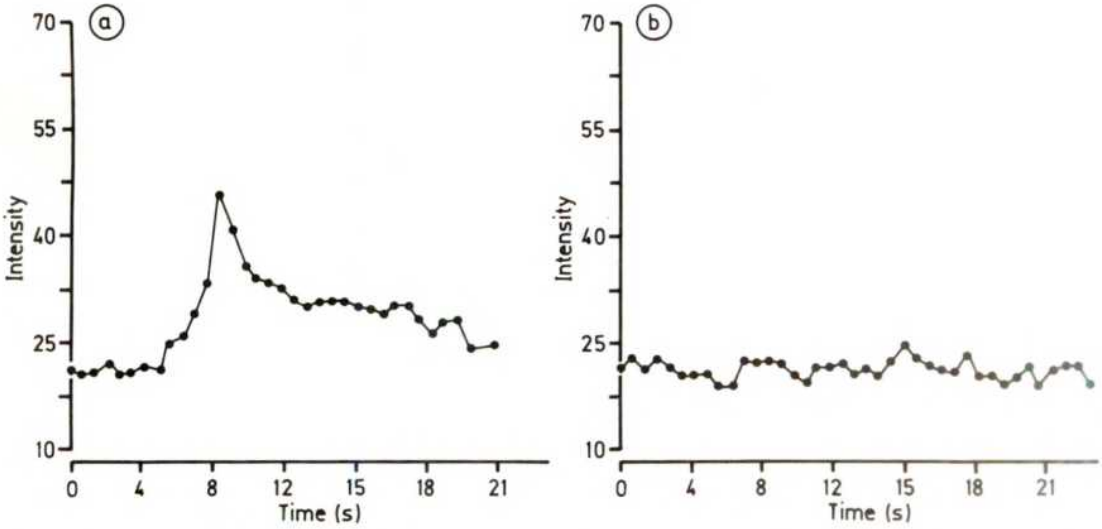

Fig 2 *Time-intensity curves of myocardial echocontrast. (a) Sharp transient increase in lateral wall videointensity during transit of echocontrast; (b) no change in septal videointensity after echocontrast injection. Intensity is displayed in arbitrary units and time in seconds (s).*

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analysis of the time-intensity curve of myocardial contrast confirmed that there was no increase in septal videointensity and a considerable transient increase in the intensity of echocontrast in the lateral wall (fig 2).

Discussion

There was a striking difference between the findings of myocardial contrast enhanced cross sectional echocardiography in both patients. Clinically and in terms of wall motion analysis they seemed to be similar: both had a history of an anteroseptal transmural myocardial infarction with ensuing apicoseptal akinesia or dyskinesia. The first patient had severe proximal double stenosis of the left anterior descending coronary artery and good contrast opacification of the septum by collaterals from the right coronary artery. The second patient had good patency of all three major epicardial coronary arteries, but he had a large perfusion defect of the whole septum and apex. The most probable explanation for this difference is that the first patient had preserved septal microcirculation and thus potential viability of the septum. The second patient had septal scar tissue without preserved microcirculation, as shown by the very poor branching of the left anterior descending coronary artery.

In our experience and that of others[6] the right coronary artery supplies the posterior aspect of the interventricular septum. This segment is not visualised in apical views and is best seen from short axis cross sections. This type of examination was not performed in the present study.

Septal wall motion is altered in patients with left bundle branch block but it is difficult to differentiate between septal scar tissue and viable septum that is dyskinetic because of the left bundle branch block. Our first patient is an example of a case of left bundle block in which myocardial contrast enhanced cross sectional echocardiography could be used to assess septal viability.

We conclude that these two cases demonstrate the potential value of myocardial contrast enhanced cross sectional echocardiography for the assessment of myocardial and collateral blood flow. Contrast enhanced echocardiography may be a useful supplement to coronary arteriography for the assessment of regional myocardial perfusion.

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Characterisation of the normal right ventricular pressure-volume relation by biplane angiography and simultaneous micromanometer pressure measurements

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SUMMARY The normal right ventricular pressure-volume relation was studied by recording biplane right ventriculograms with simultaneous high fidelity pressure recordings in 10 adults found to have normal coronary arteries and haemodynamic function at diagnostic cardiac catheterisation. Right ventricular volume was measured frame by frame from digitised ventriculograms by a modification of Simpson's rule. The accuracy of this method was tested in a study of 22 human and animal right ventricular casts. There was excellent agreement between calculated volumes and those measured by fluid displacement. The derived regression equations were used to correct right ventricular volumes calculated from in vivo studies. The mean (SD) end diastolic volume index for the group was 62 (13) ml/m^2, the stroke volume index was 43 (8) ml/m^2, and the ejection fraction was 62 (6)%. Right ventricular pressure-volume loops were generated by combining simultaneous volume and pressure curves. The normal right ventricular pressure-volume loop was triangular, departing significantly from the square or rectangle of the normal left ventricular pressure-volume loop. Ejection from the right ventricle began early during the pressure rise and continued as right ventricular pressure fell. As a result phases of isovolumic contraction and relaxation were difficult to define.

These observations show that normal right ventricular pressure-volume relations differ considerably from those of the normal left ventricle, presumably reflecting the different loading conditions of the two ventricles.

Unlike the left ventricle, the right ventricle has been largely ignored in terms of the detailed characterisation of its function. Probably the most important factor responsible for this has been the difficulty in accurately measuring right ventricular volume as a result of its complex geometric shape. Unlike the normal left ventricle, which approximates to a prolate ellipsoid, the right ventricle does not lend itself to volume calculation on the basis of a simple geometric assumption. None the less, various methods have been used, including simple area-length algorithms and geometric models[1-3] and the use of Simpson's rule, which permits the measurement of the volume of a complex shape by dividing it into a series of slices.[2 4 5] Although they require computer techniques to make such measurements practicable, methods incorporating Simpson's rule can be applied to the determination of right ventricular volume both throughout the cardiac cycle and as it is affected by disease.

Although the importance of right ventricular dysfunction in the pathogenesis of ischaemic,[6] and congenital heart disease[7] has been emphasised, most previous studies have been restricted to simple measurements of right ventricular volumes and ejection fraction. Few attempts have been made to apply to

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the right ventricle those more sophisticated indices of function that have greatly enhanced our knowledge of the left ventricle, such as data derived from ventricular pressure-volume loops. An animal study[8] and a radionuclide study in patients with acquired heart disease[9] have suggested that there may be fundamental differences between the pressure-volume relations of the normal left and right ventricles; however, the normal right ventricular pressure-volume relation has yet to be defined angiographically. This study was therefore designed to examine the normal right ventricular pressure-volume relation, using Simpson's rule to measure right ventricular volume from biplane right ventriculograms combined with simultaneous high fidelity pressure recordings.

Patients and methods

RIGHT VENTRICULAR VOLUME DETERMINATION

Right ventricular casts

Twenty two radio-opaque casts of animal (ovine, porcine $n = 16$), and human ($n = 6$) right ventricles were made with acrylic resin and radiographic contrast material. The hearts were prepared by oversewing both atrioventricular valves, and a purse string suture (placed around each great vessel) was tightened around a large bore cannula through which the resin-contrast mixture was introduced. The right and left ventricles were distended to filling pressures of 10 and 13 cm of resin and contrast mixture (equivalent to approximately 8 and 10 mm Hg respectively) in an attempt to preserve the normal geometry of the interventricular septum. The hardened cast was dissected from the right ventricle and any residual tissue was removed by immersion in concentrated sodium hydroxide. Cast volumes were determined by water displacement and the mean of five separate estimations was taken.

Angiographic volume estimation

Each cast was then placed in its anatomical position on the catheterisation table. Biplane ventriculograms were recorded on 35 mm cinefilm at 50 frames per second in anteroposterior, lateral, and 30° right anterior oblique, 60° left anterior oblique projections. Calibration was made by a modification of the linear shift method,[10] and the magnification factor was calculated from angiograms exposed before and after the cast was moved 10 cm within the *x* ray field such that:

magnification factor = observed shift/actual shift.

A single frame from each of the orthogonal views was then projected on to a Summagraphics digitising plate interfaced with a Prime 750 computer and the cast outline was traced by hand. No attempt was made to follow precisely the pattern of trabeculae or papillary muscles. Instead a smooth line was traced around the outermost perimeter of the cast silhouette. For each outline approximately 100 x,y coordinates were recorded and stored on magnetic tape for later analysis. Three dimensional reconstructions were plotted from these stored data (fig 1) by a computer program that is described in detail elsewhere.[11] We used Simpson's rule to calculate the volume of the casts. Briefly, the ventricular outline was divided into 40 equal segments along its long axis. The cross sectional area of each segment was assumed to be elliptical and the diameters of the major and minor axes were calculated from each of the angiographic views. Simpson's rule was then applied to calculate the volume of each slice, and the total volume of the ventricle according to the formula:

$$\text{Volume} = \frac{\pi h}{3}\left(\sum_{1}^{39} d1_O\, d2_O + \tfrac{1}{2}\sum_{2}^{40} d1_E\, d2_E\right),$$

where h = slice depth, d1 and d2 are the major and minor diameters respectively, and O = odd numbered slices, and E = even numbered slices.

PATIENTS

Ten adults (mean age 37 years, range 29–47, six men, four women) were studied. All were undergoing cardiac catheterisation to establish a clear diagnosis for atypical chest pain. No patient had clinical or electrocardiographic evidence of previous myocardial infarction or arrhythmia and no patient was taking regular cardiac medication. The Brompton Hospital Ethical Committee approved the study and all patients gave their informed written consent.

Cardiac catheterisation

Patients were studied without premedication. Routine left ventriculography and coronary angiography were performed from a femoral approach with the patient supine. After the demonstration of normal left heart haemodynamic function, left ventriculography, and coronary arteriography at least 15 minutes were allowed to elapse before right heart catheterisation was performed. All right heart pressures were measured by a micromanometer tipped catheter with a high-flow lumen through which angiography was performed (Millar Instruments Inc). The transducer of this catheter has a linear response with an output accuracy of ±0·5% between −50 and +300 mm Hg and a frequency response from 0 to 20 kHz. Before insertion the transducer was set at zero for the mid-chest level and calibrated to +100 mm Hg with an external cali-

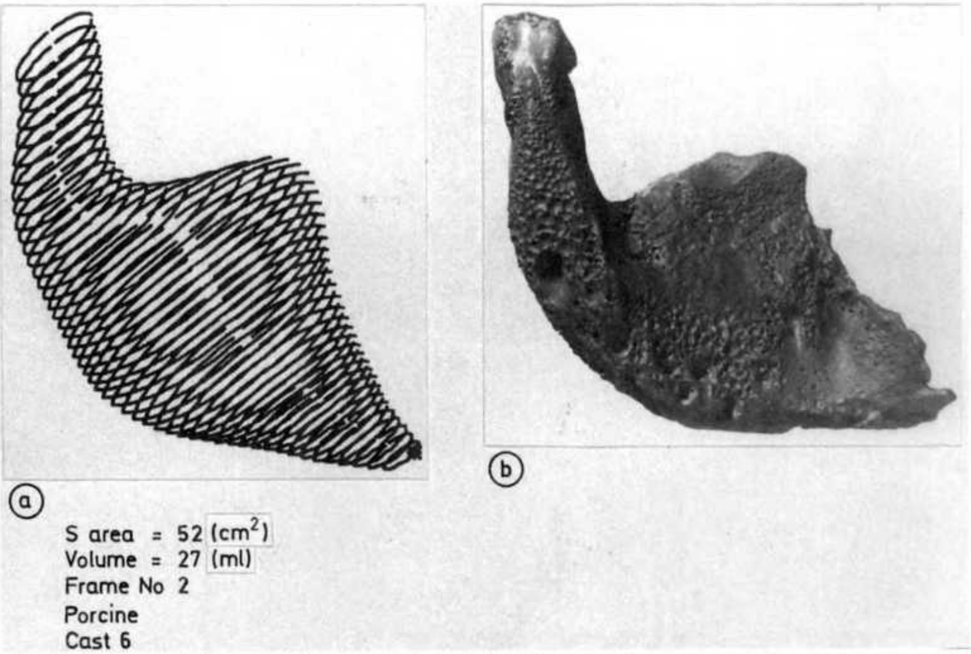

Fig 1 *Right ventricular cast and computer-derived three dimensional reconstruction from biplane angiogram.*

bration source. We took care to position the catheter tip in the apex of the right ventricle. While the patients held their breath mid-inspiration we recorded biplane right ventriculograms in anteroposterior and lateral projections on 35 mm film during the injection of 30 ml of radiographic contrast medium (Isopaque). Simultaneous recordings of right ventricular pressure were made at a paper speed of 200 mm/s and an event mark was pressed when contrast material appeared in the right ventricle. To enable exact synchronisation an electrocardiograph timing mark was recorded simultaneously on both cine and pressure recordings. At the end of the study the catheter was left in the right ventricle and the patient was shifted 10 cm in a craniocaudal direction. A cine film was recorded in both projections for later calibration.

ANALYSIS OF ANGIOGRAMS

Each view of the biplane right ventriculogram was digitised with the equipment described above. Only sinus beats were analysed; extrasystoles and post-extrasystoles were discarded. Starting at the R wave of the electrocardiogram successive frames were projected on to the digitising table and cavity outlines were traced frame by frame throughout the cycle. Once again no attempt was made to follow the trabecular pattern precisely. This procedure was repeated for the same cycle in the orthogonal view and finally the pressure curve recorded during the cycle was digitised by the same equipment, data points being extracted every 20 ms corresponding to each frame of the angiogram. All data were stored on magnetic tape and the following were derived:

(*a*) Superimposed plots of cavity outlines throughout the cardiac cycle (fig 2)

(*b*) Graphs displaying changes of cavity volume, and pressure throughout the cardiac cycle (fig 3), from which measurements of end diastolic and end systolic volumes were made and corrected for body surface area (ml/m^2). Right ventricular ejection fraction was calculated as the ratio of stroke volume to end diastolic volume.

(*c*) Pressure-volume loops showing instantaneous changes of pressure and volume throughout the cardiac cycle (figs 4 and 5), and from these loops the following measurements were made: (*i*) right ventricular ejection before and after peak right ventricular pressure expressed as a percentage of the total stroke volume; (*ii*) the external mechanical work performed by the right ventricle during systole. This is equivalent to the area enclosed by the pressure volume loop and was determined by automatic planimetry, with systolic stroke work being expressed in J/m^2 body surface area (1 mm Hg.ml = $1{\cdot}36 \times 10^{-4}$ J); and (*iii*) cycle efficiency, which was

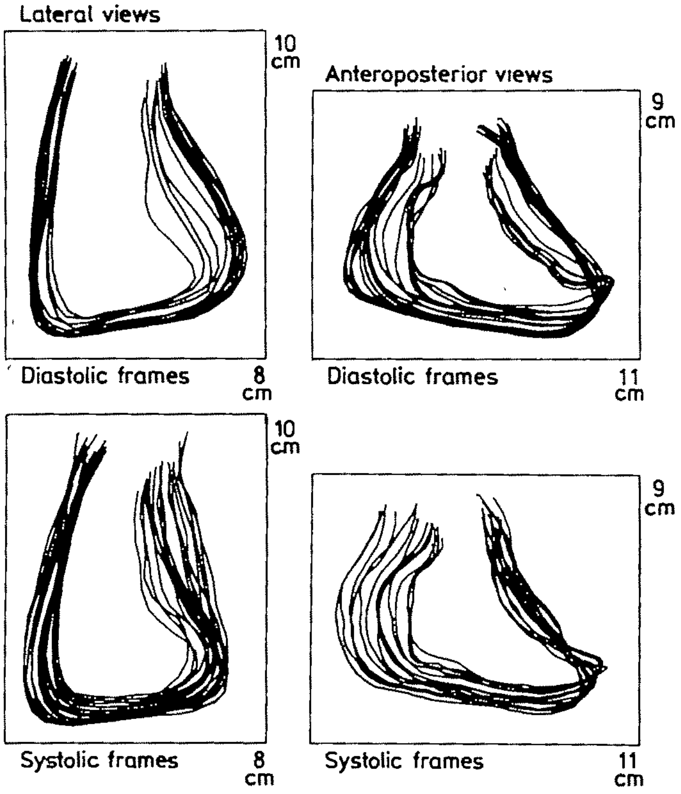

Fig 2 *Superimposed plots of cavity outlines from successive frames of each of the biplane views of a right ventriculogram.*

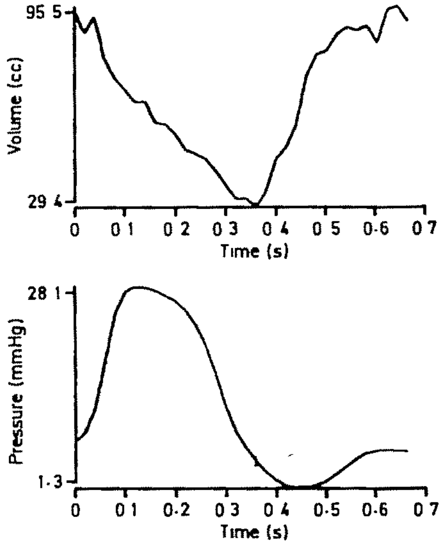

Fig 3 *Plots showing simultaneous right ventricular pressure and volume curves.*

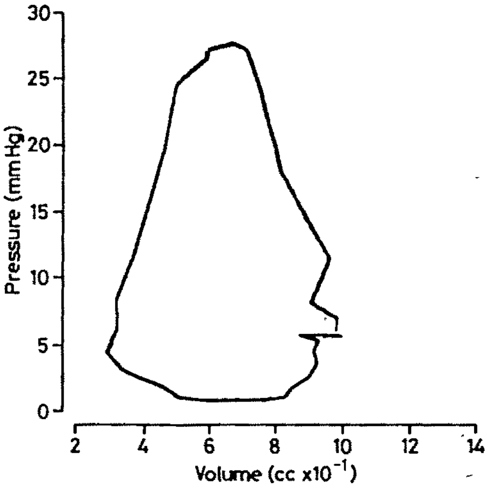

Fig 4 *Normal right ventricular pressure-volume loop derived from the curves shown in fig 3.*

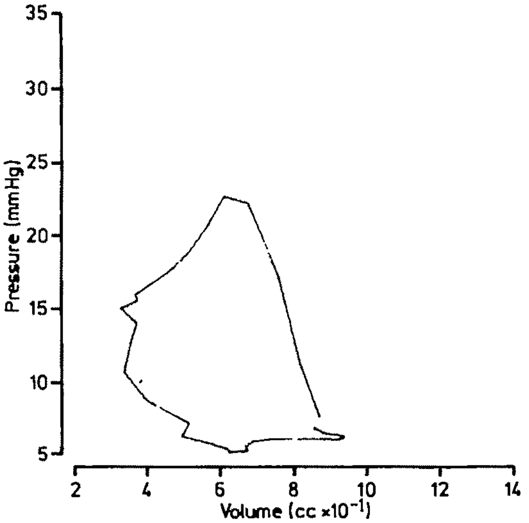

Fig 5 *Normal right ventricular pressure-volume loop. In this example there is a better defined limb of isovolumic relaxation. Maximum work 944·8 mm Hg × ml and efficiency 62%.*

measured by a method previously described for the left ventricle[12] and expressed as the ratio of the area enclosed by the loop to that of a square or rectangle that just encloses it. This represents the ratio of actual work done to the maximum possible performed by a ventricle with the same stroke volume and pressure change.

In each case the cycle was digitised on another occasion and where possible ($n = 7$) a second cycle was digitised to assess intraobserver and beat to beat variation.

STATISTICAL ANALYSIS

Group data were expressed as mean (1 SD). The actual cast volumes, measured by fluid displacement, were compared with volumes calculated by linear regression analysis by the method of least squares.

In the clinical studies intraobserver and beat to beat variability of ventricular volumes and ejection fraction were expressed as the mean percentage difference and as a coefficient of repeatability.[13] Assuming that the mean difference between the two sets of observations is zero (that is there is no systematic over or underestimation) and that the difference is unrelated to the absolute size of the measurement (for example the error does not increase with the size of the ventricle), this coefficient is equal to two standard deviations of the mean absolute difference, and is thus expressed in the same units as the original measurements.

Results

CAST DATA

The volume of the casts ranged from 10 to 91 ml. Fig 6a and b shows the relation between cast volume measured by fluid displacement and volume derived from the two pairs of orthogonal views. Excellent correlation coefficients were obtained (both $r = 0·99$), with low standard errors and Y intercepts suggesting that the method was applicable to calculation of small volumes. The regression equations for each pair of orthogonal views were: (*i*) anteroposterior and lateral views: volume (true) = 0·86 volume (calc) +0·68 (SEE = 4 ml; $p < 0·001$); (*ii*) right and left anterior oblique views: volume (true) = 0 81 volume (calc) +0·48 (SEE = 4 ml; $p < 0·001$).

PATIENT DATA

Left heart haemodynamic function and coronary arteries were normal in all patients. Peak right ventricular systolic pressure was 26 (4) mm Hg, and right ventricular end diastolic pressure was 6 (4) mm Hg. There was no angiographic evidence of tricuspid regurgitation in any of the patients. Satisfactory right ventriculograms were obtained in all, but because of technical problems such as multiple extrasystoles or poor opacification only a single beat was available for analysis in three of the 10 patients. Calculated right ventricular volumes were corrected by the regression equations shown above and expressed per square metre body surface area. End diastolic volume index was 64 (13) ml/m^2 and stroke volume index was 43 (8) ml/m^2. The mean right ventricular ejection fraction for the group was 62 (6)%.

RIGHT VENTRICULAR PRESSURE-VOLUME RELATIONS

Right ventricular pressure-volume loops tended to be more triangular than the typical left ventricular pressure-volume loop (fig 7). Ejection from the ventricle began early during pressure upstroke with a mean of 39 (4%) of the stroke volume being ejected before peak right ventricular pressure. Consequently there was a poorly defined phase of isovolumic contraction. Interestingly ejection continued well beyond the development of peak right ventricular pressure with 43 (9)% of the stroke volume being ejected during pressure fall. In only five patients was there a well defined end systolic shoulder to the loop (fig 5).

Right ventricular systolic stroke work was 0·078 + 0·021 J/m^2 per beat and the resulting cycle efficiency was 56 (8)% (normal for left ventricle = 72–84%).

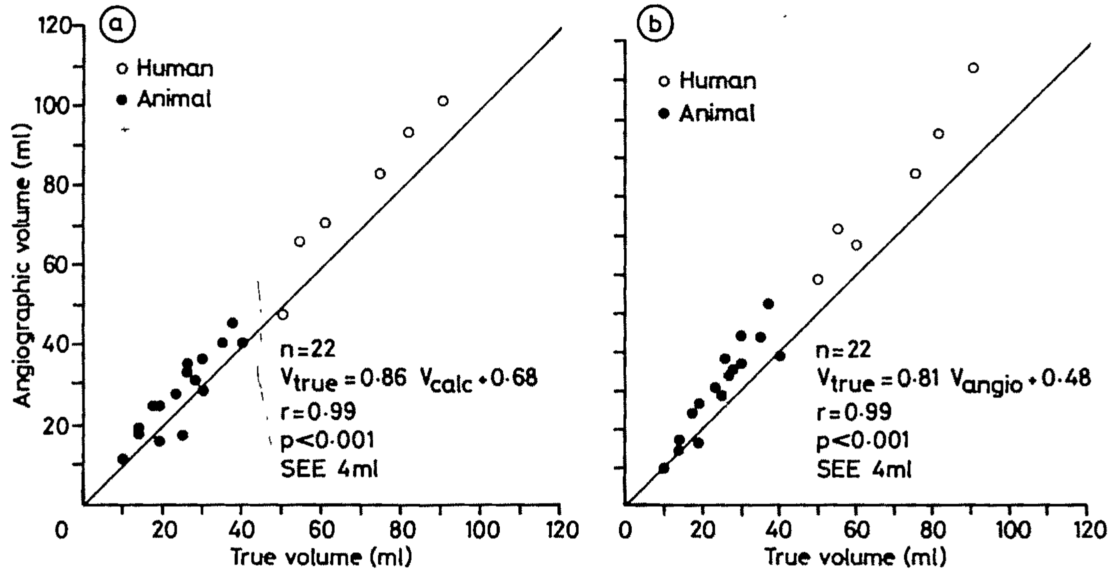

Fig 6 *Graphs showing the relation between right ventricular cast volumes measured by fluid displacement and from biplane angiograms. (a) Anteroposterior and lateral views. (b) 30° right anterior oblique and 60° left anterior oblique views.*

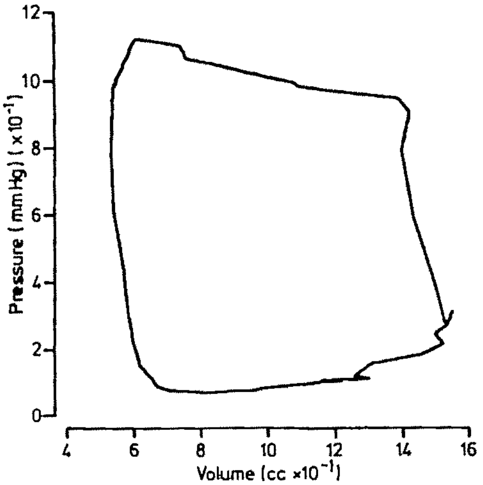

Fig 7 *Typical example of a normal left ventricular pressure-volume loop.*

INTRAOBSERVER AND BEAT TO BEAT REPRODUCIBILITY

The table shows intraobserver and beat to beat repeatability.

Table *Intraobserver and beat to beat reproducibility of measured variables*

	EDV	*SV*	*RVEF*
Intraobserver.			
Mean % difference	5 9	6 8	5 9
Coefficient of repeatability	5 2	3 6	4 0
Beat to beat (n = 7):			
Mean % difference	11 2	13 5	12 9
Coefficient of repeatability	9 2	9 8	14 0

EDV, end diastolic volume; SV, stroke volume, RVEF, right ventricular ejection fraction.

Discussion

Investigation of left ventricular pressure-volume relations has greatly increased our understanding of left ventricular function and it is perhaps surprising, therefore, that there is so little information on right ventricular pressure-volume relations. One explanation is the difficulty of accurately measuring right ventricular volume because of its complex geometry. Nevertheless, several attempts have been made.[1 3 5] Although methods based on area-length derivations and geometric models[1-3] accurately measure the volumes of casts of the right ventricle, they may be inappropriate for the measurement of right ventricular volume throughout the cardiac cycle because changes in cavity shape and spatial orientation during contraction and relaxation, and under the abnormal conditions of chronic pressure or volume overload, make it unlikely that a single geometric model can be applied in all circumstances.

Methods using Simpson's rule go some way towards overcoming these difficulties but certain geometric assumptions are inherent in any method that attempts to measure ventricular volume from angiograms. In this study we have assumed that each slice of the right ventricle is elliptical and when we digitised both the casts and ventriculograms we included papillary muscles and trabeculae in the cavity outline. It is not surprising, therefore, that our method overestimates ventricular volumes when compared with those derived from fluid displacement of the casts. None the less, this overestimation appears to be consistent and, by applying the appropriate regression equation, right ventricular volume can be estimated with a degree of accuracy approaching that previously described for the left ventricle.[14] Indeed simple measurements of end diastolic and end systolic volumes in our patients were similar to those reported by others[5 15] and the derived stroke volume index (43 (8) ml/m^2) is similar to that reported for the left ventricle.[16] Thus it should be possible to apply our technique to frame by frame analysis of right ventricular volume in a manner similar to that previously performed for the left ventricle.

Gated blood pool radionuclide angiography has been used to assess right ventricular pressure-volume relations[9] but such techniques calculate volume changes by averaging data obtained from many cardiac cycles and hence pressure and volume measurements can never be truly simultaneous. Furthermore, the relatively low sampling rate (30 frames per second) and variations in the RR interval during data acquisition introduce additional errors. In our study right ventricular volume was calculated every 20 ms and close synchronisation of pressure and volume was achieved. Beat to beat variability and intraobserver variability of measured indices were acceptable and the overall shape of the right ventricular pressure-volume loops was both reproducible and similar in all patients.

The very different loading conditions of the right and left ventricles might be expected to influence their relative pressure-volume characteristics and indeed this has been suggested by the study of cross-circulated canine right ventricles.[8] The authors of this report commented on the triangular shape of the right ventricular pressure-volume loop resulting from the continued fall in cavity volume after peak right ventricular pressure. Our study confirms these findings in human beings. Unlike the square or rectangular loop of the normal left ventricle (fig 7) in which there is little change in cavity volume during the two isovolumic periods and in which there is a well defined end systolic shoulder, we have shown that ejection from the right ventricle began during the pressure upstroke and consequently a phase of isovolumic contraction was difficult to define. The observation that ejection continued while right ventricular pressure was falling was a striking feature in our study; as much as 60% of the stroke volume was ejected after peak systolic pressure. In only five patients was there a well-defined end systolic shoulder to the pressure-volume loop.

That the right ventricle can continue to eject during a fall in pressure was suggested indirectly from observations by Shaver *et al* in 1974 who, using simultaneous right ventricular and pulmonary artery pressure measurements, described a so-called "hangout period" of up to 90 ms between right ventricular pressure fall and pulmonary valve closure in patients with normal right heart pressures.[17] The ability of the right ventricle to eject blood as cavity pressure is falling presumably reflects the low hydraulic impedance to flow and high capacitance of the normal pulmonary vascular bed since this hangout period was greatly reduced when pulmonary vascular resistance was raised. There are no human right ventricular pressure-volume data on the effect of pressure loading, but further support for this phenomenon being a load-dependent one, rather than an intrinsic property of the right ventricular myocardium, comes from similar appearances of pressure-volume loops obtained from left ventricles ejecting against the much reduced afterloads that are present after the Mustard operation (unpublished observations) and during treatment with vasodilators.[18]

The external mechanical work performed by the right ventricle on the circulation during systole is equal to the area enclosed by the pressure-volume loop.[19] The ratio of this area to the area of a square or rectangle that just encloses it represents the ratio of actual work done to the maximum possible done by a ventricle with the same pressure and volume changes and has been termed "cycle efficiency". Despite the finding that the work performed by the right ventricle in ejecting its stroke volume is considerably lower than that for the left ventricle, its "efficiency", as measured by this index, is low (58 (6)%). Cycle efficiency is, however, simply a measure of the ability of the ventricle to act as a square wave pump and the low cycle efficiency observed for the normal right ventricle should not be interpreted as a reflection of efficiency in terms of its energetics, but rather as a convenient method of quantifying the departure of the shape of its pressure-volume loop from that of a square or rectangle.

Indeed there is evidence that the right ventricle may be more efficient than the left in terms of its energetics. It has been demonstrated previously that a considerable amount of potential energy stored in the left ventricular wall at end systole is dissipated in isovolumic relaxation.[20] In experimental preparations much of this potential energy can be converted to external mechanical work by manipulating the afterload against which the left ventricle ejects.[20] Left ventricular pressure-volume loops under these circumstances are similar in shape to those we have recorded for the normal right ventricle and this suggests that the normal right ventricle may be converting more of the potential energy stored in its walls at maximum pressure into external mechanical work.

Further studies are required to evaluate the effect of loading conditions on the human right ventricular pressure-volume relation and until then the clinical implications of our results are likely to be speculative. Our observations do suggest, however, that previous measurements of isovolumic and end systolic indices of right ventricular contractility should be interpreted with caution.

We have shown that it is possible to measure right ventricular volume throughout the cardiac cycle and construct pressure-volume loops. Analysis of these loops showed fundamental differences between the pressure-volume relation of the normal left and right ventricles, which presumably reflect the low hydraulic impedance to flow in the pulmonary circulation.

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Continuous recording of coronary sinus oxygen saturation during atrial pacing in patients with coronary artery disease or with syndrome X

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SUMMARY Coronary sinus oxygen saturation was measured continuously during incremental atrial pacing in 34 patients undergoing cardiac catheterisation. In eleven patients with normal coronary arteriograms, negative exercise tests, and no ST segment depression on the electrocardiogram, an increase in the rate of atrial pacing transiently decreased coronary sinus oxygen saturation but within 20 s oxygen saturation returned to the control value. In six patients with coronary artery disease ST segment depression developed during atrial pacing. The coronary sinus oxygen saturation fell and remained reduced until pacing was discontinued. The size of the fall of coronary sinus oxygen saturation increased with increasing heart rate. In seven patients with coronary artery disease the ST segments were unaltered during atrial pacing and coronary sinus oxygen saturation did not fall. Ten patients with syndrome X were studied. In six ST segment depression developed on atrial pacing. In five, three of whom developed ST segment depression, the changes in coronary sinus oxygen saturation during atrial pacing were similar to those observed in patients without any evidence of coronary artery disease. In three, all of whom developed ST segment depression, coronary sinus oxygen saturation gradually increased throughout the period of atrial pacing. In two patients coronary sinus oxygen saturation fell in a manner similar to that observed in patients with obstructive coronary artery disease who developed ST segment depression on pacing.

Thus regulation of coronary blood flow in normal persons in response to an increase of heart rate is rapid. Oxygen extraction across the coronary bed can increase by up to 30% and a persistent increase in oxygen extraction is an indicator of myocardial ischaemia. The term "syndrome X" does not describe a homogeneous group of patients but in the majority coronary sinus oxygen saturation does not fall despite symptoms and changes on the electrocardiogram, indicating that inadequate coronary blood flow is not the dominant mechanism.

The heart is critically dependent on aerobic metabolism.[1] Oxygen extraction at rest is >55% so that a substantial increase of oxygen supply can only be brought about by an increase of coronary blood flow. Coronary blood flow can increase five times whereas oxygen extraction can increase by only a half. Although the relation between changes in coronary blood flow and myocardial oxygen consumption has been extensively investigated in animals,[2] less is known about the timing of these changes in people.

Myocardial ischaemia develops when myocardial consumption of adenosine triphosphate exceeds the rate of production possible from the oxygen available in coronary blood[3] and is initially characterised by increased glycogenolysis and lactate production. This usually occurs when myocardial work is increased and blood flow is limited by obstructive atheromatous coronary artery disease. More rarely ischaemia can result from a primary reduction of coronary blood flow caused by coronary constriction.[4] Myocardial ischaemia caused by atheromatous obstructive coronary artery disease is recognised clinically by angina pectoris, changes on the electrocardiogram, and the presence of reversible abnormalities of wall motion.

Some patients with angina pectoris have positive

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exercise tests and normal coronary angiograms.[5-7] The term syndrome X is used to describe this group.[8] The pathophysiological mechanisms underlying syndrome X are not understood.

This study was designed to investigate the relation between changes in coronary sinus oxygen saturation during atrial pacing in patients with normal hearts, coronary artery disease, or syndrome X.

Patients and methods

PATIENTS

The table shows the three groups of patients that we studied.

Group 1 consisted of eleven patients (seven men and four women, aged 39–59 years). They had recurrent atypical chest pain not responsive to nitroglycerin, normal electrocardiograms, and negative exercise tests. Echocardiograms were normal. They were undergoing cardiac catheterisation to exclude organic heart disease as a cause of their symptoms. After investigation these patients were believed to be entirely free of any form of heart disease and thus constituted a control group of patients with normal hearts.

Group 2 consisted of thirteen patients, all men, aged 39–67 years. They had typical angina pectoris on exertion and 10 had positive treadmill exercise tests (> 1 mm planar or downsloping ST segment depression 0·8 ms after the J point). All had clinically significant stenosis (> 70% reduction of diameter) of the left anterior descending coronary artery. Two had additional disease of the circumflex artery and the remaining eleven had three vessel coronary artery disease. No patient had had a myocardial infarction and there was no evidence of left ventricular hypertrophy on echocardiography.

Group 3 consisted of ten patients (five men and five women, aged 39–63 years) with exertional chest pain relieved by rest and nitroglycerin. On treadmill exercise all developed chest pain typical of angina. Nine had normal resting electrocardiograms. On

Table *Data on patients in the study*

Patient	*Age (yr)*	*Sex*	*Treatment*	*Exercise test**	*Coronary artery disease†*
1	44	M		–	N
2	58	M	N	–	N
3	40	M	BN	–	N
4	44	F		–	N
5	39	F		–	N
6	47	M		–	N
7	43	M	B	–	N
8	59	F	BC	–	N
9	53	F		–	N
10	33	M		–	N
11	39	M		–	N
12	52	M	B	+	LC
13	53	M	BC	+	LCR
14	67	M	BC	+	LCR
15	57	M	B	+	LCR
16	57	M		–	L
17	55	M	BC	+	LCR
18	56	M		–	LC
19	45	M	B	–	L
20	63	M		+	LCR
21	46	M	BCN	+	LCR
22	59	M		+	LCR
23	47	M	BN	+	LCR
24	39	M		+	LCR
25	58	F		+	N
26	47	F		LBBB	N
27	53	M		+	N
28	39	F		+	N
29	51	M		+	N
30	48	M		+	N
31	47	F	BC	+	N
32	52	M		LBBB	N
33	55	M		+	N
34	63	F		+	N

B, β-blocker; N, nitrate; C, calcium antagonist.

*–, no ST segment changes, +, ST segment depression. LBBB, left bundle-branch block; †N, normal coronary arteries, disease in left anterior descending, L; left circumflex, C; or right, R, coronary arteries HR, heart rate, CSO_2, coronary sinus oxygen saturation

exercise eight of these developed ST segment depression in at least one precordial lead and one developed left bundle branch block. One patient had left bundle branch block at rest but developed typical chest pain on exercise. All had normal coronary arteries. Chest *x* rays and left ventriculograms were normal. Echocardiography showed normal cardiac dimensions, normal valves, and no hypertrophy. Seven patients had ergometrine provocation studies at cardiac catheterisation and these did not show evidence of focal coronary constriction.

PROTOCOL

All patients were undergoing routine diagnostic cardiac catheterisation at the time of the study. They were premedicated with lorazepam (1 mg) one hour before catheterisation.

An optical fibre oxygen saturation catheter (7·5 Opticath, Oximetrix, California, USA) was inserted into the left subclavian vein and placed approximately 4 cm into the coronary sinus under fluoroscopic control. The position was checked by injection of a small quantity of radiographic contrast medium (Urografin 370). Coronary sinus oxygen saturation was measured optically by a spectrophotometric catheter oxygen saturation system (Oximetrix Inc, California, USA) and recorded continuously. A pacing electrode was inserted into the right atrium either from the left subclavian or right femoral vein. An incremental atrial pacing test[9] was performed after recording the 12 lead surface electrocardiogram. Heart rate was increased from 20 beats per minute above the resting rate by 10 beats per minute at one minute intervals. Pacing was performed for the first 50 s of each minute period, and during the last 10 s a 12 lead electrocardiogram was recorded in sinus rhythm. The pacing test was continued until a maximum heart rate of 180 beats per minute had been reached, until the development of severe chest pain, or until ST segment depression >2 mm or atrioventricular block occurred. Right ventricular pacing was performed in four patients from group 1 and in seven from group 2 according to the same protocol.

*Atrial pacing test**

Heart rate (beats/mn)		*Systolic BP (mm Hg)*		*CSO_2 (%)*		*ST segment changes*
Basal	*Maximum*	*Basal*	*At maximum heart rate*	*Basal*	*At maximum heart rate*	
Group 1						
90	180	140		38	40	–
60	140	140	155	30	29	–
75	120	120	118	24	24	–
55	120	140	150	41	42	–
90	180	135	148	34	34	–
61	150	128		44	40	–
85	170	140	152	33	36	–
64	140	100	110	22	25	–
81	180	140	158	33	32	–
79	160	130		19	20	–
74	170	130		34	34	–
Group 2						
61	160	135	150	42	38	–
70	100	125	120	31	30	–
86	110	140	140	34	35	–
61	110	135	160	32	24	+
63	150	120		28	28	–
75	170	115	120	28	26	–
71	140	100	100	40	40	–
73	150	125	150	43	42	–
72	140	130		29	18	+
68	140	125		33	24	+
70	160	130		41	10	+
81	160	130		31	14	+
89	180	135		30	14	+
Group 3						
72	170	110	135	40	46	+
64	170	135	140	31	16	LBBB
71	180	128	142	40	59	+
80	170	120	125	22	32	+
60	180	110	115	51	50	+
72	180	130	135	22	20	+
70	180	110	120	35	35	–
68	150	115	125	20	19	LBBB
69	120	132	130	30	15	–
62	140	135		26	26	+

Patients subsequently underwent coronary angiography and left ventriculography by either the Judkins' or Sones' technique. All results are expressed as mean (SEM).

Results

The table shows the details of individual patients.

Group 1

Figure 1 shows a recording of changes in coronary sinus oxygen saturation in a patient from this group undergoing atrial pacing. Mean resting heart rate was 74 (4) beats per minute (range 55 to 90) and resting coronary sinus oxygen saturation was 32 (2)% (range 19–44%). With each incremental increase in heart rate there was an initial drop in coronary sinus oxygen saturation but within 20 s it returned to the basal value (fig 1). When atrial pacing was stopped there was a rapid transient rise in coronary sinus oxygen saturation; this fell abruptly when pacing was restarted. At the end of each increase in atrial pacing coronary sinus oxygen saturation was similar to the basal level (fig 1). The maximum incremental increase in heart rate that could be achieved before the onset of atrioventricular block varied from 45 to 100 beats per minute. Resting systolic blood pressure did not change throughout the atrial pacing test (131 (4) basal and 142 (7) mm Hg at maximum heart rate). Four patients underwent right ventricular pacing to a heart rate 80 beats per minute above the resting rate. Despite a fall in systolic blood pressure from a basal level of 131 (4) to 110 (6) mm Hg ($p < 0·05$) at the maximum heart rate, coronary sinus oxygen saturation changes were similar to those seen during atrial pacing. Transient depression of the ST segments of the electrocardiogram was seen in two patients after the end of pacing.

Group 2

We saw variable responses in this group of thirteen patients. Six patients who had positive exercise tests developed pain and significant ST segment depression on atrial pacing. Figure 2 shows the response from one such patient. At heart rates up to 20–30 beats per minute above the basal rate the changes in coronary sinus oxygen saturation were similar to those seen in the control subjects. When pacing was performed at heart rates of ≥ 40 beats per minute above the resting rate, however, a different response was seen. Coronary sinus oxygen saturation rapidly fell at the onset of atrial pacing and in contrast with the control subjects in group 1 it remained significantly below the resting value until the end of atrial pacing. Oxygen extraction increased with increasing heart rate (fig 2). In seven patients significant ST segment depression did not develop during atrial pacing. In two of these seven patients, atrioventricular block developed at heart rates of 100 and 110 beats per minute. The remaining five patients, three of whom had negative exercise tests, were paced to similar heart rates as the six in whom ST segment depression did develop, but the changes in coronary sinus oxygen saturation were similar to those observed in normal subjects (group 1). There was no change in systolic blood pressure during the atrial pacing test (125 (5) basal and 134 (8) at the end of atrial pacing, $n = 7$).

In the seven patients without ST segment depression during atrial pacing right ventricular pacing was performed to a heart rate of 180 beats per minute. In contrast with the control group there was a sustained fall in coronary sinus oxygen saturation which persisted until the end of pacing. The fall in coronary sinus oxygen saturation increased with increasing heart rates. Systolic blood pressure at the maximum pacing rate was significantly lower during ventricular pacing than during atrial pacing (90 (7) *vs* 136 (9) ($p < 0·05$, $n = 6$).

Group 3

The ten patients in this group were atrially paced to

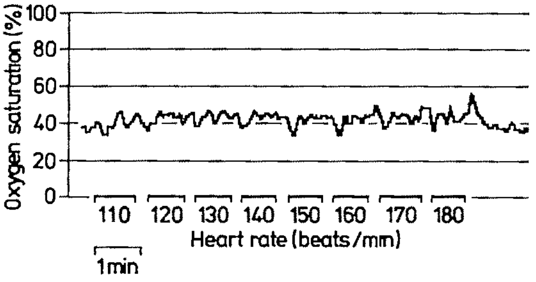

Fig 1 *Coronary sinus oxygen saturation during an incremental atrial pacing test in a patient believed to have a normal heart. Note that the saturation remained almost constant. At higher pacing rates there was a small and transient decline of saturation after the onset of pacing.*

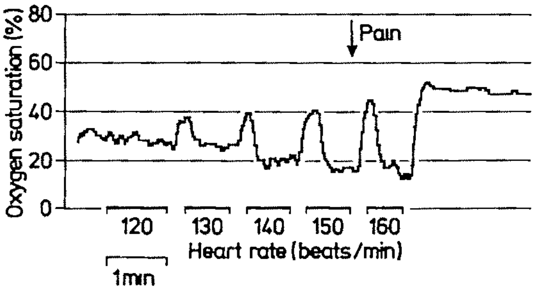

Fig 2 *Coronary sinus oxygen saturation in a patient with atheromatous obstructive coronary artery disease. The saturation fell after the onset of pacing and the fall was greater at higher heart rates.*

heart rates of between 120 and 180 beats per minute (mean 164 (21)). In five of these patients the changes in coronary sinus oxygen saturation were identical to those observed in the control subjects; three of these five patients developed > 1 mm ST segment depression during atrial pacing. In three other patients, all of whom developed ST segment depression, a different response was observed in that the coronary sinus oxygen saturation at the end of atrial pacing was higher than the resting value (fig 3). This increase varied between 6% and 20%. Two patients showed a response which was similar to that seen in the group 2 patients who developed myocardial ischaemia during atrial pacing. One of these patients had left bundle branch block at rest and the other had a normal resting electrocardiogram and developed ST segment depression on exercise testing (fig 4). This patient was severely limited by angina pectoris and he consistently developed pain on minimal exercise and when paced at only 10 beats per minute above his resting rate. Inspection of fig 4 shows that coronary sinus oxygen saturation fell and remained low throughout each increment of atrial pacing. The maximum heart rate that could be attained before severe chest pain terminated the test was 120 beats per minute and ST segment changes were not observed. Evaluation of ST segment changes in the first of these two patients was not possible because of the presence of bundle branch block.

Discussion

Coronary sinus oxygen saturation was recorded during and after atrial pacing in patients with normal hearts, coronary artery disease, or syndrome X. A fibreoptic method was used to measure oxygen saturation. The method depends on the illumination of blood by light at three selected frequencies and the sensing of the reflected light at these frequencies. The output of the analyser gave a mean for data collected over a 5 s interval. The accuracy, reliability, and stability of the recording system have been reported previously.[10] The method avoids the errors that might arise from intermittent sampling and allows rapid changes of saturation to be followed accurately. The necessity of following continuously oxygen saturation is evident from inspection of figs 1–4.

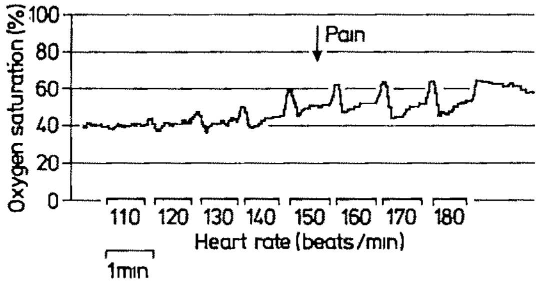

Fig 3 *Coronary sinus oxygen saturation in a patient with syndrome X. The saturation never fell below the control value and the mean rose during the test. At higher heart rates the saturation fell substantially at the onset of pacing*

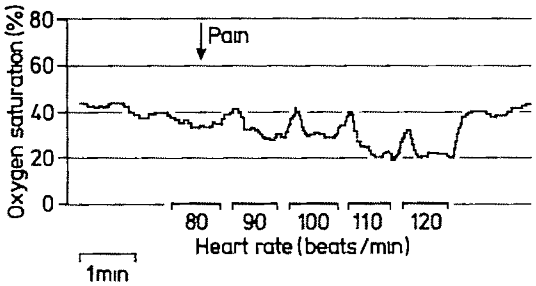

Fig 4 *Coronary sinus oxygen saturation in a patient with syndrome X. The pattern observed in this patient is similar to that in patients with obstructive coronary artery disease.*

When any variable is measured in the coronary sinus it must be remembered that the blood originates from different regions of the heart and that mixing may be incomplete. This is of particular importance when changes are measured during atrial pacing in patients with coronary artery disease. Parts of the myocardium may be rendered ischaemic whereas others are not. The relative blood flow from the two regions changes during atrial pacing and if mixing is incomplete the size of the change in oxygen saturation in the coronary sinus may be less than that if only blood from the ischaemic region had been sensed. To minimise these problems we selected patients who had left anterior descending coronary artery disease and placed the sensing catheter 4 cm into the coronary sinus.

We used atrial pacing to increase cardiac work.[9] The development of chest pain during atrial pacing has been reported as being non-specific for ischaemia.[11] None of our control patients experienced chest pain during atrial pacing whereas eight out of 13 patients with coronary artery disease did. During atrial pacing the ST segment was depressed in only six of the 13 and there was no ST segment depression in the control patients. Thus in our hands atrial pacing is a relatively insensitive means of detecting coronary artery disease as determined by ST segment depression or chest pain but is specific when a positive result is obtained. Similar findings have been reported by others and appear to be largely the result of an inability to pace at a rate sufficient to induce myocardial ischaemia before atrioventricular block occurs. Right ventricular pacing can be performed, but the interpretation of the electrocardiogram immediately after the end of pacing is complicated by persisting abnormalities of repolarisation or ischaemia caused by the fall of blood pressure and perfusion pressure in the coronary circulation. In the present study right ventricular pacing of four control patients resulted in transient ST segment depression in two whereas all seven patients with coronary artery disease developed ST segment depression.

Coronary blood flow and arterial oxygen saturation were not measured in this study, but in animals[12 13] and people[14 15] atrial pacing has been shown to increase coronary flow in normal myocardium but decrease flow in myocardium whose coronary arteries are severely obstructed by atheroma. In our study in patients with what finally were considered to be normal hearts, an increment in pacing rate was accompanied by a transient fall of saturation lasting approximately 15 s. The saturation then returned to the control value and on cessation of pacing the reverse sequence was observed. An increased heart rate increases the myocardial work and initially oxygen extraction increases. After 15 s, vasodilatation of the coronary bed occurs so that the venous saturation returns to normal and the increased oxygen consumption is provided by an increase of flow. Such rapid adjustments to coronary flow have previously been demonstrated in animals, where an increase of coronary flow can be demonstrated after a single added beat.[16] In dogs an increase of heart rate increases myocardial work and coronary blood flow so that coronary sinus oxygen is unchanged.[13] These observations are entirely compatible with the rapid metabolic control of coronary flow.[17] In individual normal patients the coronary sinus oxygen saturation in the steady state remained almost constant at a mean value of approximately 32%. The reason why this should be so is not clear but an oxygen saturation of 32% may represent the minimal value for optimum transport of oxygen into the cell.

The response to atrial pacing in patients with atheromatous obstructive coronary artery disease was similar to that in controls in the absence of ST segment depression or chest pain. In patients who developed chest pain or ST segment depression on the electrocardiogram, the coronary sinus oxygen saturation fell after an increment in pacing rate and then remained at a reduced value. The reduction of the saturation increased at higher rates of pacing. The earliest changes of saturation preceded the development of chest pain or changes on the electrocardiogram, as has been reported previously when chest pain was precipitated by vasoconstriction.[4] The probable explanation for these observations is that oxygen extraction increases after an increment in pacing but that an increase of coronary flow is not possible because flow is limited by stenoses in large coronary arteries in the presence of an almost maximally dilated distal vascular bed. If ischaemia is defined as occurring when myocardial adenosine triphosphate consumption exceeds the rate of adenosine triphosphate production that is possible from the oxygen available in coronary blood, then the presence of oxygen extraction greater than that which occurs in normal individuals demonstrates the presence of myocardial ischaemia. A maintained reduction of the coronary sinus oxygen saturation in the presence of increased myocardial work was associated with other indicators of ischaemia. This observation reinforces the idea that active control mechanisms maintain the coronary sinus oxygen saturation at a value of approximately 32%.

The term "syndrome X" has been used to describe very different groups of patients.[5-8 18-33] For the purposes of this study syndrome X was defined as a clinical syndrome consisting of angina pectoris, normal coronary arteriograms, and a positive exercise test. The inclusion of a positive exercise test in the definition is crucial. We have included two patients with heart block because although the exercise electrocardiograms could not be interpreted the patients developed reproducible and typical angina pectoris on the treadmill. Many studies of patients with chest pain and normal coronary arteries have not required a positive exercise test. The exercise test has been reported as positive in only a proportion of patients, for example 12/19,[6] 2/50,[33] 2/26,[18] 1/6,[24] 1/7,[25] 19/19,[21] and 2/13.[31] If this requirement is omitted then more patients will be included who have genuinely non-cardiac reasons for chest pain, such as oesophageal disease[31 32] or musculoskeletal abnormalities.[31] The differing characteristics of patients admitted to studies of patients with normal coronary angiograms almost certainly account for the widely differing frequency of oesophageal disease and ventricular dysfunction.

Many mechanisms for syndrome X have been put forward including impaired coronary vasodilator reserve,[6 7] disease of small vessels (disease of vessels beyond the resolution of coronary angiography),[24 28] epicardial-endocardial redistribution of blood flow,[26] and myocardial cell abnormalities.[6 25] Disease of small vessels has been shown only in patients with evidence of cardiomyopathy, hypertrophy, decreased ventricular compliance, and negative exercise tests.[24] That patients with syndrome X develop myocardial ischaemia is suggested by the demonstration of perfusion defects[22] and ventricular wall motion abnormalities on exercise[19] although others, in differently defined groups of patients, have been unable to show a change in left ventricular function by continuous monitoring of pulmonary end diastolic pressure.[23] The presence of ischaemia has also been claimed because changes of the ST segment were detected during 24 h monitoring of the electrocardiogram.[21] Equating ST segment changes with myocardial ischaemia is as yet unjustified, except in patients with known coronary artery disease and angina pectoris.[34] ST segment changes are common in patients with cardiomyopathy, hypertrophy, or on treatment with digoxin. The ST segment may alter on exercise or over 24 h in a substantial proportion of apparently normal persons.[35] ST segment changes are not therefore always synonymous with myocardial ischaemia, and even left ventricular dysfunction does not necessarily imply ischaemia since there are many other mechanisms for such abnormalities.

We measured the coronary sinus oxygen saturation in ten patients with syndrome X. All except two developed ST segment changes on the exercise test. One of these had left bundle branch block at rest. The other developed left bundle branch block on exercise. Both had typical and reproducible chest pain on exercise. No patient was diagnosed as having overt cardiomyopathy and none had hypertrophy of the myocardium. In two out of the ten patients with syndrome X the coronary sinus oxygen saturation changed with a pattern similar to that observed in patients with known atheromatous coronary artery disease. Since the coronary angiograms were normal these patients may either have had vasoconstriction on exercise[36] and atrial pacing or have disease of the small vessels. In the other eight patients coronary sinus oxygen never fell and in three it rose. Since six out of eight of these patients had changes on the electrocardiogram and chest pain similar to the group of patients with known coronary artery disease it is difficult to argue that these patients had myocardial ischaemia in the sense defined above. It is conceivable that the endocardium became ischaemic and the epicardium was abundantly perfused so that the mixed venous blood in the coronary sinus had a normal oxygen saturation. Such a phenomenon would be a form of "steal" except that the epicardial bed would have an excessive flow and a high venous oxygen saturation. If that were the explanation then ventricular dysfunction should be evident on exercise and in the majority of these patients no abnormality of ventricular function has been described.[23]

Alternative mechanisms may account for syndrome X. The syndrome could be caused by an increased retention of potassium in the extracellular space between cells.[37] Potassium is lost from the normal heart as heart rate increases[38] and in response to other stimuli. If this potassium could not freely exchange with the vasculature, potassium would accumulate and bring about the changes on the electrocardiogram that the physician might mistakenly interpret as ischaemia.[39] A rise of extracellular potassium concentration can largely account for the change in the configuration of the action potential[40 41] and by causing the depolarisation of pain sensors it could account for the onset of chest pain. The reason for the accumulation of potassium in the tissue may be minor changes of anatomy as presumably are present in hypertrophied myocardium or in the cardiomyopathic heart where ST segment depression is known to occur on exercise in the absence of obstructive coronary disease.

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Occurrence and clinical significance of endocardial late potentials and fractionations in idiopathic dilated cardiomyopathy

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SUMMARY In order to assess the occurrence and clinical significance of abnormal electrograms in idiopathic dilated cardiomyopathy, endocardial electrode mapping during sinus rhythm and programmed ventricular stimulation were performed in 52 patients with or without clinical ventricular tachycardia. Abnormal endocardial electrograms were recorded in 77% of the patients and were diffusely distributed over the entire left ventricular endocardium. No relation could be established between the occurrence of late potentials or fractionations and clinical or induced arrhythmias. Endomyocardial biopsy samples were taken from 20 patients and showed that reduced myofibril volume fraction was related to the occurrence of abnormal endocardial electrograms. Neither induced arrhythmias nor the presence of late potentials or fractionations identified patients who died of sudden cardiac death during the mean (SD) follow up of 33 (11) months.

Thus abnormal endocardial electrograms recorded during sinus rhythm in idiopathic dilated cardiomyopathy may only be interpreted as being a sign of damage to the myocardial cells.

Left ventricular endocardial electrode mapping was developed as a means of locating the origin of ventricular tachycardia before resection. So far most of those investigated by this technique have been patients with coronary artery disease with and without a history of ventricular tachycardia or myocardial infarction,[1-3] patients with a normal left ventricle,[4 5] with conduction defects,[6] and with hypertrophic cardiomyopathy.[7] There are limited data on patients with idiopathic dilated cardiomyopathy.[8]

It has been suggested that endocardial delayed electrical activity represents an electrophysiological predisposition to ventricular slow conduction. Because slow conduction is regarded as the prerequisite for reentry, and recurrent ventricular tachycardia is probably a reentrant arrhythmia, the detection of delayed electrical activity was assumed to distinguish patients with ventricular tachycardia from those without.[9]

Ventricular arrhythmia is common in patients with dilated cardiomyopathy.[10-12] Many of them die suddenly and unexpectedly.[13 14] Little information is available about the relation of abnormal endocardial electrograms to clinical and induced arrhythmias in this disease. Furthermore, there is uncertainty about the prognostic importance of these findings.

This prospective study was performed in unselected patients with idiopathic dilated cardiomyopathy. We tried to answer the following questions. (*a*) How common are abnormal endocardial electrograms in idiopathic dilated cardiomyopathy? (*b*) Are these signs associated with clinical and induced ventricular arrhythmias? (*c*) Can their occurrence be related to histological and morphological findings? (*d*) What is the prognostic importance of these abnormal endocardial electrograms?

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Patients and methods

STUDY POPULATION

The study population consisted of 52 patients (44 men and eight women; mean age of 49 (23–67). The diagnosis of idiopathic dilated cardiomyopathy was based on the following criteria:

(*a*) clinical symptoms or signs of congestive heart failure that is ⩾class II of the New York Heart Association.

(*b*) Echocardiographical and radiological evidence of cardiomegaly (cardiothoracic ratio >0·5).

(*c*) Reduced left ventricular ejection fraction.

(*d*) Absence of coronary artery disease confirmed by selective coronary angiography.

(*e*) Absence of valve lesions except for mild and moderate mitral regurgitation.

(*f*) Absence of specific heart muscle disease, general systemic disease, hereditary and familial disorders, systemic hypertension, or cor pulmonale.

(*g*) Positive histological and morphological findings in cardiac biopsy specimens.

All patients had normal concentrations of serum electrolytes. Antiarrhythmic treatment had been discontinued for at least three days before the investigations. No patient was on amiodarone at that time. All patients were informed of the purpose of the study and gave their written consent.

CLINICAL AND HAEMODYNAMIC FINDINGS

Seventeen (33%) patients were classified as New York Heart Association functional class II, 29 (56%) as class III, and six (11%) as class IV. The mean (1 SD) left ventricular ejection fraction at cardiac catheterisation was 38 (13)%.

The electrocardiograms taken at rest showed atrial fibrillation in 12 patients (23%) and sinus rhythm in 40 (77%). Intraventricular conduction delay was present in 25 patients (49%). Eighteen (35%) had complete left bundle branch block, four (8%) left axis deviation, and three (6%) right bundle branch block. Electrocardiographic signs of left ventricular hypertrophy were seen in 19 (37%) and of hypertrophy of both ventricles in 11 patients (21%).

CLINICAL ARRHYTHMIAS

Fourteen (27%) patients had a history of sustained ventricular tachycardia confirmed either by an electrocardiogram taken at rest, a 24 hour ambulatory electrocardiogram, or on the electrocardiograph monitor in the intensive care unit. In all of them complex ventricular arrhythmias were also seen during 24 hour ambulatory monitoring at the beginning of the study. Of the remaining 38 patients, 19 (37%) had 2–472 (median 20) episodes of non-sustained ventricular tachycardia consisting of 3–20 consecutive ventricular extrasystoles at a rate of 150–210 per minute. The other 19 patients showed no ventricular tachycardia: in five of them, 1–27 episodes of ventricular bigeminy were seen during monitoring, five had multiform and five uniform single ventricular extrasystoles and only three showed no ventricular arrhythmias at all. Patients with atrial fibrillation had a lower grade of arrhythmias. Only one of them had multiform ventricular extrasystoles and ventricular bigeminy.

No relation was found between the impairment of left ventricular function and the occurrence or complexity of ventricular arrhythmias. The patients with clinical sustained ventricular tachycardia had a mean (1SD) ejection fraction of 38 (13)%, in those with non-sustained tachycardia it was 35 (13)%, and in patients without such arrhythmias it was 41 (11)%.

PROGRAMMED VENTRICULAR STIMULATION

Programmed stimulation was performed at the right ventricular apex. The stimulation protocol included the application of one and two premature extrastimuli during sinus rhythm and at five basic driven cycle lengths (S_1S_1:600, 500, 428, 375, 330 ms). Furthermore, incremental pacing with 250 beats/min for 6 s and 250–300 beats/min for 12 s was performed. The end point of testing was either the initiation of sustained ventricular tachycardia or refractoriness.

The induced ventricular responses were defined as follows: *short ventricular response*, initiation of 2–4 consecutive non-paced ventricular extrasystoles; *non-sustained ventricular tachycardia*, initiation of ⩾5 extrasystoles with a rate of ⩾100 beats/min, lasting ⩽30 s, and with no intervention required for termination; *sustained ventricular tachycardia*, initiation of ventricular extrasystoles with a rate of ⩾100 beats/min, lasting >30 s or requiring termination by programmed stimulation or cardioversion before then because of deterioration in haemodynamic function.

ENDOCARDIAL CATHETER MAPPING

After cardiac catheterisation and before programmed ventricular stimulation, endocardial electrode mapping of the left ventricle was performed during sinus rhythm. Figure 1 shows the mapping scheme used. In each patient endocardial electrograms were recorded from 8–12 (mean 10) different catheter positions. The recording period at each site was 15–30 s with the mapping electrode in a stable position. A fixed gain (1 mm ≃ 40 mV) and band pass filtering of 50–500 Hz were used.

The abnormal endocardial electrograms were

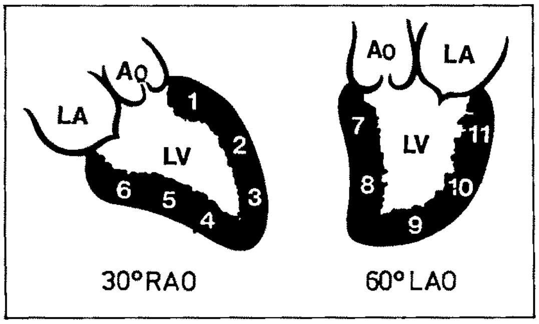

Fig 1 *Mapping scheme for endocardial catheter mapping. The 11 sites represent segmental areas of the left ventricle (LV) determined by 30° right anterior oblique (RAO) (sites 1–6) and 60° left anterior oblique (LAO) projection (sites 7–11). 1 = anterobasal, 2 = anteromedial, 3 = anteroapical, 4 = inferoapical, 5 = inferomedial, 6 = inferobasal, 7 = septobasal, 8 = septoapical, 9 = posterolateral apical, 10 = posterolateral medial, 11 = posterolateral basal. LA, left atrium, AO aorta.*

defined as follows: *late potential,* well defined local deflection with an amplitude $\geqslant 100\ \mu V$ $\geqslant 100$ ms after the beginning of the QRS complex (that is after the J point); *fractionation,* polyphasic primarily low amplitude deflection lasting $\geqslant 50$ ms.

ENDOCARDIAL BIOPSY

Immediately after the electrophysiological studies or the day after cardiac catheterisation, biopsy samples were taken from the left ventricular wall of 20 patients by means of the King's College bioptome. The technique for estimating the volume fraction of myofibrils has been described in detail elsewhere.[15]

FOLLOW UP

The patients were followed up over a mean (1SD) period of 33 (11) (9–48) months. All patients with ventricular tachycardia and four out of five with ventricular bigeminy were treated with antiarrhythmic drugs at normal dosages, independent of the response to programmed ventricular stimulation (propafenone (median dose 600 g), amiodarone (median dose 300 g), mexiletine (median dose 600 g); quinidine (median dose 1000 mg); flecainide (median dose 300 g); sotalol (160 mg); disopyramide (600 mg)). Treatment was started empirically and monitored by 24 hour ambulatory electrocardiography. Patients attended as outpatients. If this was not possible, their referring physicians were contacted. Sudden cardiac death was defined as cardiac death within an hour of the onset of new symptoms.

STATISTICAL ANALYSIS

Data were expressed as mean (1SD), or, when they had an asymmetrical distribution, as median and range. Statistical methods included χ^2 analysis, the Wilcoxon U test for independent samples, and the H test of Kruskal and Wallis. P values of <0 05 were regarded as significant for two tailed tests.

Results

PROGRAMMED VENTRICULAR STIMULATION

A repetitive ventricular response was induced in 28 (54%) patients. In 20 (39%) patients there were short responses and in eight (15%) patients ventricular tachycardia; this was sustained in three and non-sustained in five. The rate of the tachycardia was >200 beats per minute in six of the eight patients. In no case was ventricular fibrillation induced directly.

The impairment of left ventricular function did not influence the result of programmed stimulation. The left ventricular ejection fraction in patients with a negative result was 37 (12)%, in patients with 2–4 induced ventricular extrasystoles it was 40 (12)%, and patients with inducible ventricular tachycardia had a mean ejection fraction of 38 (17)%.

CLINICAL AND INDUCED ARRHYTHMIAS

No clear correlation was found between the number of ventricular extrasystoles induced by programmed stimulation and the type of clinical arrhythmia; except that the induction of sustained ventricular tachycardia was only seen in patients who had sustained ventricular tachycardia clinically (table 1).

ENDOMYOCARDIAL BIOPSY

An endomyocardial biopsy specimen was obtained from 20 patients. None of the biopsy samples showed any evidence of myocarditis or myocardial storage disease. In 11 patients the volume fraction of myofibrils was $\leqslant 60\%$, and in nine it was $>60\%$. The clinical characteristics of the patients undergoing endomyocardial biopsy were no different from those of the whole study population. Left ventricular ejection fraction and the frequency of clinical or

Table 1 *Results of programmed ventricular stimulation in relation to clinical arrhythmias*

	Repetitive ventricular response			
	0 (%)	*2–4 (%)*	*>5 (%)*	*Total (%)*
Sustained VT	5 (36)	6 (43)	3 (21)	14 (100)
Non-sustained VT	7 (37)	10 (53)	2 (10)	19 (100)
No VT	12 (63)	4 (21)	3 (16)	19 (100)
Total	24 (46)	20 (39)	8 (15)	52 (100)

VT, ventricular tachycardia.

Table 2 *Clinical characteristics of 20 patients from whom endomyocardial biopsy samples were taken and the corresponding myofibril volume fraction*

	Myofibril volume fraction		
	≤60% (n = 11)	*>60% (n = 9)*	*Total (n = 20)*
LVEF (%)	37 (15)	38 (13)	37 (14)
Clinical arrhythmia:			
Sustained VT	1	3	4
Non-sustained VT	6	2	8
No VT	4	4	8
RVR:			
0	5	3	8
2–4	6	5	11
≥5	—	1	1

LVEF, left ventricular ejection fraction; VT, ventricular tachycardia, RVR, repetitive ventricular response.

induced arrhythmias (table 2) were no different in patients with a volume fraction of myofibrils ≤60% and those with a volume fraction >60%.

ENDOCARDIAL ELECTRODE MAPPING DURING SINUS RHYTHM

Endocardial electrograms of the left ventricle were obtained from 513 electrode positions from biplanar right and left anterior oblique projections. Abnormal electrograms were recorded in 40 patients (77%). Twenty eight (54%) patients showed late potentials and 12 (23%) showed late potentials and fractionations. Late potentials had a median amplitude of 340 μV (100–500 μV); the median duration of fractionations was 95 ms (range 55–270 ms).

Table 3 shows the frequency of late potentials and fractionations in relation to the mapping site at which they were recorded. Late potentials were found at 161 of 513 electrode positions whereas fractionations were only seen in 16 electrode positions. Both signs of delayed electrical activity were distributed over the entire endocardium of the left ventricle without being concentrated at any one site.

ABNORMAL ENDOCARDIAL ELECTROGRAMS AND CLINICAL ARRHYTHMIAS

The occurrence of abnormal endocardial electrograms was not associated with a higher grade of ventricular arrhythmia (fig 2). Five (36%) of 14 patients with sustained ventricular tachycardia had normal endocardial electrograms; whereas only one (5%) patient without clinical tachycardias did not have late potentials or fractionations.

ABNORMAL ENDOCARDIAL ELECTROGRAMS AND INDUCED ARRHYTHMIAS

There were no significant differences in the occurrence of abnormal endocardial electrograms between patients with induced ventricular tachycardia, those with short repetitive responses, and those in whom the response to programmed stimulation was negative (table 4). In 20 of 40 patients with abnormal endocardial electrograms, no ventricular response could be induced; whereas, in two patients with normal endocardial electrograms, ventricular tachycardia was induced and in six short responses were initiated. All patients in whom sustained ventricular

Table 3 *Occurrence of endocardial late potentials (LP) and fractionations (FR) at different left ventricular mapping sites in relation to the total number of electrode positions*

Mapping site	*LP*	*FR*	*Table (%)*	*No of catheter positions (100%)*
		Right anterior oblique		
1	15	4	19 (35)	55
1–2	7	—	7 (54)	13
2	22	4	26 (36)	73
2–3	10	—	10 (53)	19
3	17	—	17 (36)	47
3–4	8	—	8 (47)	17
4	17	1	18 (40)	45
4–5	4	1	5 (63)	8
5	18	3	21 (40)	52
5–6	8	—	8 (30)	27
6	35	3	38 (24)	157
Total	161	16	177 (35)	513
		Left anterior oblique		
7	8	1	9 (15)	61
7–8	8	—	8 (27)	30
8	20	5	25 (33)	76
8–9	9	1	10 (28)	36
9	41	—	41 (46)	90
9–10	15	1	16 (62)	26
10	33	4	37 (41)	91
10–11	11	2	13 (34)	38
11	16	2	18 (28)	65
Total	161	16	177 (35)	513

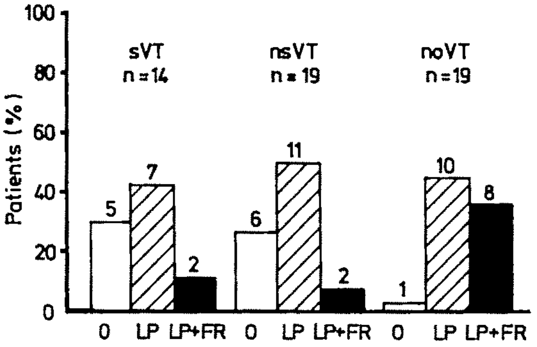

Fig 2 *Endocardial late potentials (LP) and fractionations (FR) in relation to clinical arrhythmias. sVT, sustained ventricular tachycardia, nsVT, non-sustained ventricular tachycardia.*

tachycardia was induced had abnormal endocardial electrograms.

ABNORMAL ENDOCARDIAL ELECTROGRAMS AND ENDOMYOCARDIAL BIOPSY

Fourteen (70%) of the 20 patients who had endomyocardial biopsy showed abnormal endocardial electrograms. The distribution of late potentials and fractionations was similar to that of the whole study population.

The volume fraction of myofibrils had a significant effect on the presence of endocardial late potentials and fractionations. Ten (91%) of 11 patients with a myofibril volume fraction of <60% had abnormal endocardial electrograms, whereas only four (44%) out of nine patients with a volume fraction >60% did (p < 0·05) (fig 3).

Table 4 *Results of programmed ventricular stimulation in relation to the presence of endocardial late potentials (LP) and fractionations (FR)*

	Repetitive ventricular response			
	0	*2–4*	*≥5*	*Total (%)*
No LP or FR	4 (33)	6 (50)	2 (17)	12 (100)
LP	16 (57)	7 (25)	5 (18)	28 (100)
FR	4 (33)	7 (58)	1 (9)	12 (100)
Total (%)	24 (46)	20 (39)	8 (15)	52 (100)

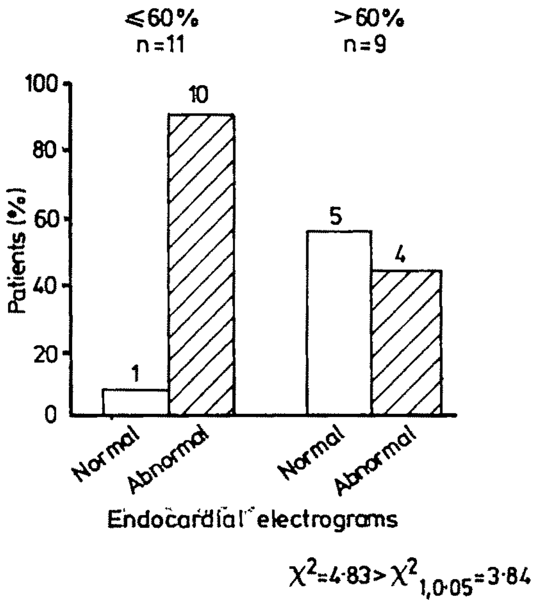

Fig 3 *Occurrence of abnormal endocardial electrograms in relation to the volume fraction of myofibrils in endomyocardial biopsy samples taken from 20 patients.*

FOLLOW UP

During a mean follow up of 33 (11) months, nine (17%) patients died: five of congestive heart failure, three of sudden cardiac death, and one from immunological complications after a cardiac transplant. The mean survival time (from the beginning of the study) was 15 (10) (1–25 months). Antiarrhythmic management was similar in patients who died and those who survived.

All patients who died had a significantly reduced left ventricular ejection fraction (≤40%) (p < 0·02). Three of five patients who died of congestive heart failure and all three with sudden cardiac death had clinical ventricular tachycardia. Programmed ven-

Table 5 *Clinical characteristics of patients who died of sudden cardiac death (SCD) or of congestive heart failure (CHF) and of those who survived*

	No	*Age (y) (mean (SD))*	*LVEF (%) (mean (SD))*	*sVT (%)*	*nsVT (%)*	*RVR ≥5*	*LP*	*LP+FR*
Survivors	42	47 (13)	40 (13)*	11 (26)	14 (33)	7 (17)	23 (55)	10 (24)
Dead								
SCD	3	57 (4)	27 (7)	1 (33)	2 (67)	—	1 (33)	1 (33)
CHF	5	49 (15)	31 (9)	2 (40)	1 (20)	—	3 (60)	1 (20)

*p < 0 02 *vs* those who died.
Two patients who underwent a cardiac transplant were excluded.
LVEF, left ventricular ejection fraction; sVT, sustained ventricular tachycardia, nsVT, non-sustained ventricular tachycardia;
RVR, repetitive ventricular response; LP, late potential; FR, fractionation.

tricular stimulation induced a short response with three consecutive extrasystoles in one of the patients with sudden cardiac death and in two of the five who died of congestive heart failure. In all other patients who died, the response to programmed ventricular stimulation was negative. The incidence of abnormal endocardial electrograms was not significantly different in patients who died and those who survived (table 5).

Discussion

Endocardial catheter mapping is a newer method for evaluating abnormal endocardial electrograms. Recent studies in patients with recurrent ventricular tachycardias have focused on abnormal endocardial electrograms as the electrophysiological basis for these rhythm disturbances. So far a preponderance of patients with coronary artery disease have been investigated. Little information is available on the occurrence and clinical significance of abnormal endocardial electrograms in idiopathic dilated cardiomyopathy.

CLINICAL AND INDUCED ARRHYTHMIAS

Like others, we confirmed that ventricular arrhythmias are common in idiopathic dilated cardiomyopathy; and like Huang *et al*[10] and Meinertz *et al*[11] we did not find a correlation between a reduced left ventricular ejection fraction and clinical tachycardia.

There was a poor correlation between clinical and induced arrhythmias. Meinertz *et al* used the same stimulation protocol in 42 patients with dilated cardiomyopathy.[16] Fifteen had clinical ventricular tachycardia, but ≥6 ventricular extrasystoles could not be induced in any of them. None the less, they induced ventricular tachycardia in three out of 27 patients with low grade arrhythmias. Cassidy *et al* investigated 26 patients with idiopathic dilated cardiomyopathy in a study population of 158 patients.[8] They used a stimulation protocol of up to three extrastimuli. Twenty four of 26 patients had confirmed ventricular tachycardia or cardiac arrest. Ventricular tachycardia (≥3 extrasystoles) or ventricular fibrillation was induced in 68%. Thus the reproducibility of clinical ventricular tachycardia in idiopathic dilated cardiomyopathy is lower than in coronary artery disease.[17]

ABNORMAL ENDOCARDIAL ELECTROGRAMS AND CLINICAL ARRHYTHMIAS

Abnormal endocardial electrograms were recorded in 77% of our study population. Fifty four per cent had late potentials and 23% had both late potentials and fractionations. A low incidence of fractionated activity was recently reported by Cassidy *et al*[8]—fractionated electrograms lasting ≥70 ms were found in only 12%. Waxman and Sung[18] and Josephson *et al*[19] reported on individual patients with idiopathic dilated cardiomyopathy and recurrent sustained ventricular tachycardia. In both of them the endocardial electrograms were abnormal.

Although we often saw abnormal endocardial electrograms and ventricular arrhythmias, there was no clear correlation between these two findings.

ABNORMAL ENDOCARDIAL ELECTROGRAMS AND INDUCED ARRHYTHMIAS

We found that endocardial late potentials or fractionations did not influence the result obtained with programmed ventricular stimulation. Only when patients had clinical and induced sustained ventricular tachycardia was it possible to consider late potentials as the electrophysiological basis for the arrhythmia. But such an interpretation must be qualified, because in two patients without late potentials or fractionations non-sustained ventricular tachycardia was induced and in 20 patients with abnormal endocardial electrograms the response to programmed ventricular stimulation was negative. In Cassidy *et al*'s study fractionated activity was only seen in patients with induced sustained ventricular tachycardia.[8]

ABNORMAL ENDOCARDIAL ELECTROGRAMS AND ENDOMYOCARDIAL BIOPSY

The striking result was that patients with a myofibril volume fraction of ≤60% had a significantly higher occurrence of abnormal endocardial electrograms. The signs of delayed electrical activity were not concentrated at any particular site.

Studies of endomyocardial biopsy specimens have shown that the myofibril volume fraction determined in one biopsy sample is representative of the rest of the heart.[20] The conclusion is that both abnormal endocardial electrograms and the reduced volume fraction of myofibrils are expressions of damage to myocardial cells.

PROGNOSTIC SIGNIFICANCE OF ELECTROPHYSIOLOGICAL FINDINGS

The main causes of death in idiopathic dilated cardiomyopathy are intractable congestive heart failure and sudden cardiac death.[13 14 21] Like other studies[11 12 22] we found that compared with those who survived, patients who died during the mean follow up of 33 (11) months had a significantly reduced left ventricular function. There was no difference in ventricular function between patients who died of sudden cardiac death and those who died of congestive heart failure.

Cases of sudden cardiac death could not be clearly identified by clinical arrhythmias in life. All of these patients had clinical ventricular tachycardia, but the presence of ventricular tachycardia in dilated cardiomyopathy did not identify patients with an increased risk of sudden cardiac death. Von Olshausen *et al* reported similar results.[12] During a mean follow up of 12 (5) months, three out of 60 patients died suddenly; two of them had ventricular bigeminy. Neri *et al* recently confirmed this result.[22]

The result obtained from programmed ventricular stimulation with up to two extrastimuli was not a reliable method of predicting sudden cardiac death. Ventricular tachycardia had not been induced in any of the cases of sudden cardiac death. In the study of Meinertz *et al*, seven of 42 patients died during the follow up of 16 (7) months; two of sudden cardiac death. No patient had inducible ventricular tachycardia.

As far as we know there are no data on whether abnormal endocardial electrograms in idiopathic dilated cardiomyopathy are of prognostic importance for sudden cardiac death. In our study population, the frequency of abnormal endocardial electrograms was similar in these cases and in those who died of congestive heart failure and in those who survived.

Figulla *et al* recently pointed out that a reduced myofibril volume fraction was the most significant factor that influenced the haemodynamic course—deterioration, stabilisation, or improvement.[15] Because a myofibrillar volume fraction of $\leqslant 60\%$ was more common in patients with abnormal endocardial electrograms, it might be that these findings are also related to a deterioration of haemodynamic function. This assumption is only speculative because only two of the patients who died had had an endomyocardial biopsy, and this relation was found in only one. On the other hand, two patients who died (one of sudden cardiac death and one of congestive heart failure) had normal endocardial electrograms. Further studies are required to establish whether abnormal endocardial electrograms identify patients with dilated cardiomyopathy whose haemodynamic function will worsen.

Conclusion

Abnormal electrograms recorded by means of endocardial electrode mapping during sinus rhythm are common in patients with dilated cardiomyopathy. We found there is no clear correlation between their occurrence and clinical or induced ventricular arrhythmias. Abnormal endocardial electrograms do not seem to be of prognostic value for sudden cardiac death. Therefore, it is doubtful whether they represent the electrophysiological basis of ventricular arrhythmias in dilated cardiomyopathy. Our results suggest that they may merely be a sign of myocardial damage.

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Electrocardiographic findings in myotonic dystrophy

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SUMMARY Sixty five patients with myotonic dystrophy, from a defined population in northern Sweden with an extremely high prevalence of this disease, were examined by electrocardiography. The patients were subdivided into three groups according to the severity of the disease. Abnormal electrocardiograms were found in 6 (35%) patients with mild disease, 12 (50%) patients with moderate disease, and 23 (96%) patients with severe disease. First degree atrioventricular block and left anterior hemiblock were the most commonly encountered abnormalities in patients with mild and moderate disease, whereas atrial fibrillation and flutter, abnormal Q waves, and repolarisation abnormalities were more common in patients with severe disease.

This study shows that the heart is often affected by myotonic dystrophy. These effects can be detected by electrocardiography in early and mild forms of the disease. The effect on the heart is progressive and clinically important atrial arrhythmias and electrocardiographic abnormalities which are useful in differential diagnosis are common in severe forms of the disease.

Myotonic dystrophy is a multisystemic disease which is inherited in an autosomal dominant fashion at a locus on chromosome 19.[1] Myotonia and devastating muscle atrophy are characteristic features, but other organ systems may also be affected and the clinical presentation is variable. Some individuals manifest the full range of skeletal, cardiac, and smooth muscle abnormalities as well as skeletal changes, cataracts, endocrine dysfunction, and mental retardation. Others have only cataracts or an individual symptom complex such as heart disease or dysphagia.[2] Experimental and clinical data suggest that myotonic dystrophy represents a genetically induced primary alteration in the structure and function of cellular membranes, but the specific metabolic defect has not been defined.[3] It has recently been proposed that myotonic dystrophy may represent not one isolated entity but a class of genetic defects having a similar clinical expression.[4]

There is electrocardiographic evidence of heart disease in most patients with myotonic dystrophy.[5] Although abnormalities do not produce symptoms in most patients, some show severe symptoms as a result of conduction and rhythm abnormalities. Thus well documented cases of complete atrioventricular block and malignant ventricular arrhythmias have been reported.[6 7] Echocardiographic and radionuclide angiocardiographic studies have shown impaired left ventricular function[8 9] but symptomatic cardiac failure is an uncommon feature of the disease.[5] A high frequency of mitral valve prolapse has been reported in myotonic dystrophy[10] but the existence of a causal relation has recently been questioned.[11]

Information on the course of the heart disease and its relation to the severity of neuromuscular symptoms is still sparse,[12] and the reported frequency of various electrocardiographic abnormalities varies considerably.[5 11 13] Available data are, however, based on small series of patients in varying stages of the disease and besides, some workers have focused only on arrhythmias and conduction disturbances and less attention has been paid to signs indicating myocardial damage and repolarisation abnormalities.

We have assessed the frequency of all types of electrocardiographic alterations in patients with myotonic dystrophy. Because the prevalence of the disease was high in the population we examined, we were able to study a large number of cases.

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Patients and methods

We studied 65 consecutive patients with the diagnosis of myotonic dystrophy investigated at either the County Hospital, Boden, or the County Hospital, Luleå, Sweden, from 1980 to 1986. These two hospitals serve a region in the coastal region of Norrbotten, the northernmost county in Sweden, with 95 000 inhabitants. The diagnosis of myotonic dystrophy was based on neuromuscular investigation and confirmatory electromyography when the clinical findings were equivocal. Only patients with a positive family history, distinct myotonia, and distal muscular weakness were included. To avoid chance inclusion of patients with asymptomatic coronary artery disease and age related degenerative disease of the cardiac conduction system we excluded men aged >50 and women aged >60. None of the patients included in the study had heart disease of other causes or was on medication with drugs known to induce electrocardiographic changes.

The severity of the disease was classified on the basis of the patient's ability to perform those daily activities that can be limited by neuromuscular symptoms: mild, subjective symptoms but no functional disturbances; moderate, functional disturbances but the patient is able to undertake all activities of daily life and is able to do a light job; severe, major functional disturbances with the patient being incapable of undertaking most daily activities.

A 12 lead electrocardiogram (I, II, III, −aVR, aVL, aVF, V1–V6) with the conventional amplification (1 mV = 10 mm) was recorded at a paper speed of 50 mm/s. All electrocardiograms were evaluated independently by two clinical physiologists. If they did not agree on the interpretation a third reading was conducted together with a cardiologist. The evaluation included a classification according to the Minnesota code[14] of arrhythmias, P wave amplitude, atrioventricular and intraventricular conduction defects, Q and QS patterns, hypertrophy patterns, ST depression/elevation, and T wave features. We used the criteria of Castellanos and Lemberg for hemiblocks[15]. A broadened P wave was defined as > 0·13 mm. The QT interval was corrected for differences in heart rate by a modification of Bazett's formula ($QTc = QT/\sqrt{RR}$, where the QTc interval is the corrected value of the QT interval and RR is the cardiac cycle length).[16] QTc values of 0·44 s for men and 0·46 s for women were used as upper limit of normal. Q waves and repolarisation alterations were classified as abnormal or possibly abnormal. Recordings with a prolonged QT interval or a broadened P wave were classified as abnormal. The prevalence of various electrocardiographic abnormalities was compared with results in a normal population.[17] Age standardized rates[18] were calculated with the age distribution in the entire series as the standard.

Results

We studied 65 patients (33 men and 32 women). The mean age for the series was 37·2 years. Table 1 shows the distribution of patients according to the severity of the disease. There were 17 patients (26%) with mild, 24 (37%) with moderate, and 24 (37%) with severe disease. There were more men than women in the group with mild disease and more women than men in the group with severe disease. The mean age of the patients was 31·4 years in the group with mild disease, 37·4 years in the group with moderate disease, and 41·1 years in the group with severe disease.

Table 2 shows the electrocardiographic findings in the entire series of patients and in each of three patient groups with varying severity of disease. Electrocardiograms with at least one abnormal feature were found in 41 (63%) of 65 patients, while alterations classified as possibly abnormal were found in another five (8%). The proportion of recordings showing abnormalities increased with the severity of the disease and was 35% in mild disease, 50% in moderate disease, and 96% in severe disease. The remarkable features are the high frequency of abnormal electrocardiograms in the entire series of patients and the concentration of cases with atrial fibrillation and flutter, abnormal Q waves, and repolarisation abnormalities in the subset of patients with the most severe form of systemic disease. Table 3 shows the distribution according to age and severity of the disease and age standardised frequency rates of individuals with an abnormal electrocardiogram. The proportion of abnormal electrocardiograms also increased with the severity of neuromuscular symptoms after standardisation for age.

Sinus rhythm was present in all patients with mild, in 96% of patients with moderate, and in 67% of patients with severe disease. Atrial fibrillation or

Table 1 *Patients with myotonic dystrophy. distribution by age, sex, and severity of disease*

				Age (yr)	
Severity of disease	*No*	*M*	*F*	*Mean (SD)*	*Range*
Mild	17	14	3	31·4(11·6)	17–52
Moderate	24	13	11	37·4(13·2)	19–57
Severe	24	6	18	41·1(11·9)	24–59
Total	65	33	32	37·2(13·9)	17–59

Table 2 *Electrocardiographic findings in 65 patients with myotonic dystrophy*

	Severity of disease			
	Mild	*Moderate*	*Severe*	*Total*
Complete ECG evaluation:	*(n = 17)*	*(n = 24)*	*(n = 24)*	*(n = 65)*
Abnormal ECG	6 (35%)	12 (50%)	23 (96%)	41 (63%)
Suspected abnormal ECG	2 (12%)	2 (8%)	1 (4%)	5 (8%)
Rhythm				
Sinus rhythm	17 (100%)	23 (96%)	16 (67%)	56 (86%)
Atrial fibrillation	0	0	2	2 (3%)
Atrial flutter	0	1	4	5 (8%)
Pacemaker	0	0	2	2 (3%)
AV and IV block *	*(n = 17)*	*(n = 24)*	*(n = 22)*	*(n = 63)*
First degree AV block	3 (18%)	5 (21%)	5 (23%)	13 (21%)
LAH	2 (12%)	3 (13%)	6 (27%)	11 (18%)
LPH	0	1	0	1
RBBB	1	1	1	3
LBBB	0	2	0	3
Atypical BBB	0	1	3	4
LAH + RBBB	0	0	0	0
First degree AV block + IV block	1	3	4	8
P waves:†	*(n = 17)*	*(n = 23)*	*(n = 16)*	*(n = 56)*
Broadened P waves	0	2 (9%)	1 (6%)	3 (5%)
Q waves‡:	*(n = 16)*	*(n = 20)*	*(n = 18)*	*(n = 54)*
Abnormal	1 (6%)	5 (25%)	9 (50%)	15 (28%)
Abnormality suspected	1 (6%)	0	1 (6%)	2 (4%)
Repolarisation abnormalities.‡	*(n = 16)*	*(n = 20)*	*(n = 18)*	*(n = 54)*
ST elevation				
Abnormal	1	1	0	2 (4%)
Abnormality suspected	0	1	1	2 (4%)
ST-T depression				
Abnormal	0	1	7	8 (15%)
Abnormality suspected	0	0	0	0
Flattened T waves				
Abnormal	1	1	0	2 (4%)
Abnormality suspected	1	1	1	3 (6%)
Negative T waves				
Abnormal	0	0	5	5 (9%)
Abnormality suspected	0	0	0	0
Prolonged QT interval	0	0	3 (17%)	3 (6%)

*Those with pacemakers excluded; †those with pacemaker, atrial fibrillation, and atrial flutter excluded; ‡those with pacemaker and bundle branch block excluded.
AV, atrioventricular, IV, intraventricular; LAH, left anterior hemiblock; LPH, left posterior hemiblock; RBBB, right bundle branch block; LBBB, left bundle branch block.

flutter occurred in one (4%) of the patients with moderate and in six (25%) of the patients with severe disease. Two patients, both belonging to the subset of patients with severe disease, had had a pacemaker implanted: one because of sinus node dysfunction and symptomatic bradycardia and the other because of complete atrioventricular block and Adams-Stokes attacks.

Table 3 *Distribution of 41 patients with abnormal electrocardiograms according to age and severity of disease*

	Severity of disease			
Age group (yr)	*Mild (n = 6)*	*Moderate (n = 12)*	*Severe (n = 23)*	*Total (n = 51)*
29	2	3	3	8
30–39	2	2	6	10
40–49	2	5	2	9
50–59	0	2	12	14
Age-standardised rate	0 42	0 52	0·96	0·63

Conduction defects were found in 27 (42%) of the patients in the entire series. First degree atrioventricular block and left anterior hemiblock were the abnormalities most often encountered in patients with mild disease, and four of six recordings classified as abnormal in this group showed one of these two alterations. The frequency of first degree atrioventricular block was similar in all three groups, whereas the frequency of left anterior hemiblock, bundle branch block, and combined atrioventricular block and intraventricular conduction defects increased with the severity of the disease. Second degree atrioventricular block was not found in any of the recordings.

Abnormal Q waves and repolarisation abnormalities were sought on electrocardiograms without pacemaker induced rhythm or bundle branch block and were classified as abnormal or possibly abnormal. There were abnormal Q waves in 15 (28%) of 54 recordings and another two showed Q waves that were possibly abnormal. The site of the abnormal Q waves was anterior in nine cases, inferior in five, and lateral in one. The occurrence of abnormal Q waves increased with the severity of the disease: it was 6% in mild, 25% in moderate, and 50% in severe disease.

Abnormalities of repolarisation, such as ST elevation, ST-T depression, flattened T waves, and negative T waves, were found in 17 (32%) of 54 individuals, while another four (6%) showed alterations suggestive of such an abnormality. ST-T changes were most common in patients with severe disease. A prolonged QT interval was found in three patients; all had severe disease.

A pattern typical of right or left ventricular hypertrophy was not found in any of the recordings, and a broadened P wave was found in three. Five patients had solitary supraventricular and ventricular extrasystoles.

Discussion

Although cardiac abnormalities have been recognised for many years in patients with myotonic dystrophy the pathogenesis remains unknown.[2] Histopathological studies of the heart are limited and the reported non-specific findings vary from normal structure to atrophy of myocardial muscle, diffuse myocardial fibrosis, fatty infiltration, and focal myocarditis.[19-21] The course of heart disease in myotonic dystrophy has been studied in only a limited number of patients,[12] and no close correlation between the presence of cardiac abnormalities and the severity of the systemic disease has been reported. In several cases cardiac abnormalities were reported before any other manifestation of the disease developed.[13]

Only a few patients with myotonic dystrophy are reported to have cardiac symptoms, and our findings accord with those of others. In Church's review of published cases 16% of 317 patients had cardiac symptoms, which were attributable to arrhythmias in half the cases.[5] Patients with myotonic dystrophy, however, have a higher frequency of sudden unexpected death than the general population; it has been suggested that this is owing to malignant arrhythmias or high grade conduction defects.[2]

Previous studies also show that electrocardiographic alterations are common in myotonic dystrophy, but reported figures on the frequency of abnormal electrocardiograms in patients with this disease range from 45 to 85%.[5 22] These figures are based on single cases, small scale studies, and a few series on 20–30 patients[11 13 23] To date the most comprehensive review of the subject was Church's report of electrocardiographic changes in 14 of his own cases and 222 cases from 48 published reports in which 85% of the cases showed electrocardiographic abnormalities.[5] Such reviews may be biased towards the inclusion of abnormal cases and may overestimate the frequency of electrocardiographic abnormalities. Direct comparisons of frequency figures between various studies are difficult because different criteria may have been used to classify electrocardiographic changes and because patients in varying stages of the disease will have been included. Also some workers have focused on arrhythmias and conduction abnormalities only, and less attention has been paid to QRS configuration and changes in repolarisation. The commonest electrocardiographic abnormality in several reports is first degree atrioventricular block followed by various types of intraventricular conduction defects and atrial arrhythmias, in particular atrial fibrillation and flutter.

In the present study patients with myotonic dystrophy were classified according to the severity of the disease and the frequency of abnormal electrocardiograms correlated with the severity of the disease. Mean age increased with the severity of the disease and this may be a confounding variable, despite the upper age limits of the group that we studied. Nevertheless, age standardised frequency rates also correlated with disease severity, which strongly indicates that the cardiac disease in myotonic dystrophy is progressive.

Suggested causes of sudden unexpected death in myotonic dystrophy, in which the frequency of first degree atrioventricular block and bundle branch block is so high, are conduction defects progressing to complete atrioventricular block and terminating in asystole or ventricular fibrillation. A serial electrophysiological study has shown a progressive dysfunction of the His-Purkinje system,[11] but there are only a limited number of cases with complete atrioventricular block in published reports.[6] Our findings of an increasing frequency of intraventricular conduction defects as disease severity and age of the patients increases support the hypothesis that the conduction disturbances are progressive. Conduction abnormalities are not common in other myotonic disorders, and thus the finding of conduction abnormalities may be of additional diagnostic value in myotonic dystrophy.

Dysfunction of the sinus node was the underlying abnormality in one of our patients who had required the implantation of a pacemaker. Although bradycardia was the first sign of cardiac dysfunction to be described in a patient with myotonic dystrophy,[24] there are few reported cases of symptomatic sinus node dysfunction.[25 26] Five of twenty patients with normal heart rate who had an electrophysiological investigation had an abnormal sinus node recovery time.[23] There are too few histopathological studies of sinus node tissue to permit conclusions.

Abnormal Q waves without concomitant coronary artery disease or myocardial infarction are well known electrocardiographic findings in several neuromuscular disorders such as Duchenne muscular dystrophy and Friedreich's ataxia. Pseudo-infarction patterns in myotonic dystrophy have previously been reported in only a few cases. Abnormal Q waves were present in four of 27 cases reported by Viitasalo *et al*[23] and in five of 25 cases reported by Perloff *et al.*[11] In our study the Minnesota code was used to classify alterations in QRS configuration and recordings showing pacemaker induced rhythm and bundle branch block were excluded from this analysis. We found definitely abnormal Q waves in 28% of the patients in the entire series and suspected abnormal Q waves in another 4%. In those with the most severe disease an abnormal Q wave was present in 50% of the recordings and this was the most common electrocardiographic abnormality. We believe that myotonic dystrophy should be added to the list of metabolic and neuromuscular disorders in which Q waves are abnormal. The consequences of failure to recognise such a possibility may be serious.

We found ST-T alterations, classified according to the Minnesota code into abnormal changes or changes suspected of being abnormal, in 17 (32%) and four (7%) patients respectively, after the exclusion of recordings showing pacemaker rhythm and bundle branch block. Also these electrocardiographic changes seemed to be associated with severe neuromuscular symptoms, and were found only occasionally in patients with mild or moderate disease. There is little information in published reports about ST-T changes in myotonic dystrophy, and our findings suggest that a low frequency should be expected in series of patients in which most have mild or moderate disease. In Church's review ST-T changes were found in 42 of 236 patients, but the type of changes or the grounds for classification were not stated.[5] In the series presented by Perloff *et al*[11] and Viitasalo *et al*[23] ST-T changes were not reported. The QT interval was prolonged in three cases in our study; all had severe symptoms. The QT interval in myotonic dystrophy was analysed by Viitasalo *et al.*[23] They found a higher frequency (33%), of prolonged QT interval than we did. The clinical importance of a prolonged QT interval lies in its association with malignant ventricular arrhythmias, and the occurrence of this electrocardiographic alteration may be of prognostic importance in patients with myotonic dystrophy.

Atrial fibrillation or flutter was found in 10–21% of patients with myotonic dystrophy.[5 11] We found these arrhythmias in 11% of the entire series and in 25% of those with severe neuromuscular symptoms.

Extrasystoles were seen occasionally in five recordings in the present series, but a study like this, based on short recordings of resting electrocardiograms, will give little information about the true frequency of extrasystoles and intermittent arrhythmias.

The mechanisms by which electrocardiographic changes are brought about in patients with myotonic dystrophy are unknown and remain speculative. We believe that progressive, genetically induced, alterations in the structure and function of cellular membranes in myocardium, the specialised conduction system, and the autonomic nerves may prove to be of primary importance.

Myotonic dystrophy has often been described as a rare disease: reported prevalence ranges from 2·4 to 5·5 per 100 000 inhabitants.[1] The fact that as many as 65 patients could be included in the present study indicates a prevalence of at least 70 per 100 000 in this region in Northern Sweden. Such a high prevalence of myotonic dystrophy has, to our knowledge, not been reported before. An epidemiological study of myotonic dystrophy including the population in the two northernmost counties in Sweden has started in our hospitals.

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Latent pre-excitation: exposure of anterograde accessory pathway conduction during atrial fibrillation

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SUMMARY In three patients anterograde conduction across a previously undocumented accessory pathway was exposed by the development of atrial fibrillation. This unusual presentation illustrates the possible unmasking of the Wolff-Parkinson-White syndrome by other factors in patients who have not previously demonstrated the potential for anterograde accessory pathway conduction.

Atrial fibrillation is a known but uncommon feature of the Wolff-Parkinson-White syndrome. Classically patients who develop this arrhythmia have overt pre-excitation on the resting 12 lead electrocardiogram. In some individuals, however, conduction across the accessory pathway may not be seen during sinus rhythm. Under certain circumstances—for example with delayed atrioventricular nodal conduction or after premature atrial stimuli—anterograde accessory pathway conduction may become evident. We report three patients in whom pre-excitation was not visible on the resting electrocardiogram but when atrial fibrillation was seen anterograde accessory pathway conduction was exposed, with rapid ventricular rates.

Case reports

CASE 1

A 25 year old man who presented with a seven year history of palpitation had experienced several episodes of near syncope. The history and physical examination were otherwise normal.

Although the resting electrocardiogram was normal on most occasions, a single recording showed an atrial extrasystole with a pattern suggesting pre-excitation. There was a rapid ventricular response (about 200/min) with broad QRS complexes consistent with anterograde conduction across an accessory pathway during paroxysmal atrial fibrillation (fig 1).

At electrophysiological study there was no pre-excitation in control recordings but incremental right atrial pacing at rates above 120/min and pacing from the coronary sinus at rates faster than that of the sinus node produced evidence of pre-excitation. The accessory pathway was localised to the left lat-

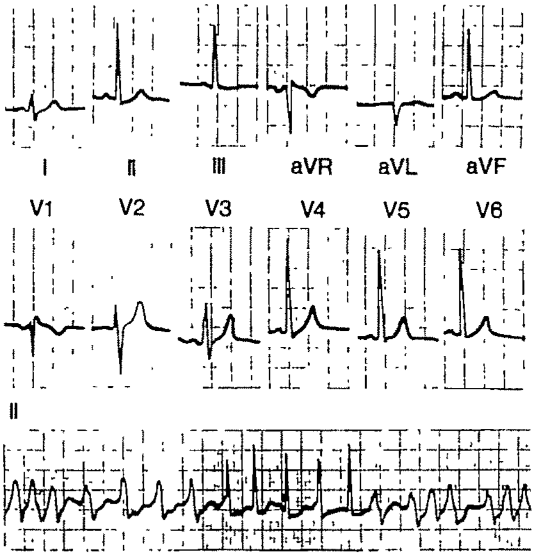

Fig 1 *Twelve lead electrocardiogram and rhythm strip showing considerable pre-excitation during atrial fibrillation with no delta waves in sinus rhythm.*

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eral wall of the heart. At operation, it was interrupted by endocardial dissection.[1] During follow up (six months) there has been no recurrence of arrhythmia.

CASE 2

A 47 year old woman with mitral stenosis and aortic regurgitation who had previously undergone closed mitral valvotomy presented with a two year history of recurrent palpitation. The resting electrocardiogram showed no evidence of pre-excitation but a tracing during paroxysmal atrial fibrillation showed a rapid ventricular response (about 280/min) with broad QRS complexes reflecting anterograde conduction across an accessory pathway (fig 2). At electrophysiological study a left lateral accessory pathway was demonstrated. At operation the accessory pathway was ablated with a cryoprobe[2]; at the same time the mitral valve was repaired and considerable left atrial enlargement was confirmed. Nine years later she remains symptom free with a normal resting electrocardiogram and no evidence of recurrent mitral valve disease.

CASE 3

A 23 year old woman had a nine year history of regular palpitation. Resting electrocardiograms were normal but pre-excitation became apparent during paroxysmal atrial fibrillation (ventricular rate 240/min). Electrophysiological study showed enhanced atrioventricular nodal conduction with a short AH interval (55 ms) which did not increase significantly during rapid atrial pacing[3] though pre-excitation then became obvious. At operation a left lateral accessory pathway was ablated by endocardial dissection.[1]

Discussion

The Wolff-Parkinson-White syndrome is characteristically associated with reentrant atrioventricular tachycardia. Atrial fibrillation and flutter occur less frequently—in 10–32% of cases.[4] The potential importance of atrial arrhythmias depends on the rapidity of anterograde conduction of atrial impulses across the accessory pathway to the ventricles, and the possibility that this might precipitate ventricular fibrillation.[5] In the Wolff-Parkinson-White syndrome anterograde conduction via the accessory pathway is usually evident in sinus rhythm because there is simultaneous conduction down the atrioventricular node, producing the classic fusion complex. Even in the absence of overt pre-excitation an accessory pathway may only be capable of retrograde conduction—and thus of maintaining reentry atrioventricular tachycardia (so-called concealed pre-excitation).[6]

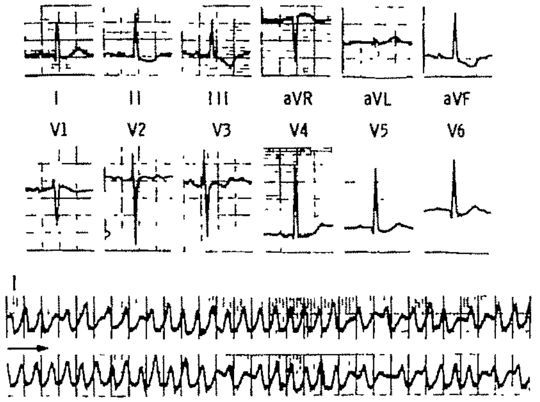

Fig 2 *Twelve lead electrocardiogram and rhythm strip showing pre-excited ventricular complexes during atrial fibrillation. There are no delta waves on the resting electrocardiogram but P mitrale is present.*

Our patients failed to display resting pre-excitation despite the presence of pathways capable of rapid anterograde conduction. Factors that may be relevant to this were the left lateral site of the accessory pathway in all three patients, the increased left atrial size in the second patient, and accelerated atrioventricular nodal conduction in case 3. Thus in all three patients the distance between the sinus node and the area of atrial input into the accessory pathway may have been sufficient to favour conduction via the atrioventricular node. The relative conduction time between the sinus node and the accessory pathway was even greater in case 2 because of left atrial enlargement and in case 3 accelerated conduction via the atrioventricular node probably made the use of the accessory pathway even less likely.

Owing to several spatial and electrical factors a normal electrocardiogram may be seen even though there is an accessory pathway capable of anterograde conduction. In principle, if the time taken for propagation of a sinus impulse to and across the accessory pathway is greater than the time taken for that impulse to propagate to the ventricles via the atrioventricular node pre-excitation may not be seen. Such conditions may occur with a left lateral pathway,[7] delay in intra-atrial conduction time,[8] or increased left atrial size. Alteration in pacemaker site to an area further from the accessory pathway[9] or slow conduction across the accessory pathway[10] may also be important. Evidence that contrary autonomic influence on accessory pathway and atrioventricular nodal conduction may also have a role comes from the finding that carotid sinus pressure can enhance and atropine diminish the degree of pre-excitation.[11] Similarly, if enhanced atrioventricular conduction or an atrionodal bypass tract is also present,[12] the sinus impulse arriving at the accessory pathway may find the ventricles already depolarised, or the accessory pathway may have been rendered refractory by concealed retrograde conduction into it from the atrioventricular node.[13] Conversely, the slowing[11] or the removal[8, 14] of atrioventricular nodal conduction may expose anterograde conduction across an accessory pathway.

The onset of atrial fibrillation may disturb this balance of relative anterograde conduction, the homogeneous origin of atrial impulses cancelling out intra-atrial differences in conduction time. Yahini and his colleagues[15] reported on one patient with paroxysmal atrial fibrillation but no pre-excitation in sinus rhythm, who was otherwise indistinguishable from five others with atrial fibrillation and the Wolff-Parkinson-White syndrome. In other cases[8] [10] coexistent mitral valve disease was present or the distance between the sinus node and the accessory pathway was thought to be responsible for lack of resting pre-excitation in sinus rhythm.[16]

Where the QRS complex is normal in sinus rhythm but there is documented supraventricular tachycardia and suspicion of an accessory pathway or when anterograde conduction is abolished by ajmaline or procainamide,[17] the patient is conventionally regarded as being at low risk of rapid conduction across the accessory pathway in atrial fibrillation. Drug-induced abolition of resting pre-excitation has been thought to preclude the development of dangerously high ventricular rates in response to atrial fibrillation.[17] Such tests have limitations,[16] however, and in one patient pre-excitation was abolished by ajmaline but at electrophysiological study the ventricular rate during atrial fibrillation was more than 300/min. Reflex changes associated with the flushing and dizziness after intravenous ajmaline and procainamide may increase anterograde atrioventricular nodal conduction and mask, rather than block, anterograde conduction in the accessory pathway.

The term "latent pre-excitation" has been used previously to describe the absence of expression of pre-excitation, whatever the cause, in the presence of an accessory pathway.[6] It might be useful to restrict it to cases in which anterograde conduction is usually masked but which may become manifest under certain circumstances, as opposed to those in which anterograde transmission across an accessory pathway is impossible at all times (concealed), owing to the presence of permanent unidirectional block or an extremely long anterograde refractory period.

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Epidural spinal electrical stimulation in severe angina pectoris

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SUMMARY The short term effects of epidural spinal electrical stimulation were studied in 10 patients with angina pectoris of New York Heart Association functional class III or IV. The antianginal pharmacological treatment given at entry to the study was regarded as optimal and was not changed during the study. The effects of epidural spinal electrical stimulation were measured by repeated bicycle ergometer tests. Treatment with epidural spinal electrical stimulation increased the patients' working capacity, decreased ST segment depression, increased time to angina, and reduced the recovery time. The observed effects did not seem to be correlated with any changes in myocardial oxygen demand during epidural spinal electrical stimulation and were additional to the benefits of the pharmacological treatment.

Patients with severe angina pectoris treated with transcutaneous electrical nerve stimulation had a reduction of chest pain, an increase in working capacity, and a reduction in ST segment depression.[1] Some patients had skin irritation of different kinds and in some the stimulation equipment restricted physical activity. These patients were offered the opportunity to test epidural spinal electrical stimulation by a fully implanted system. Epidural spinal electrical stimulation has been used successfully to treat chronic intractable pain and peripheral vascular disease.[2]

We have assessed the clinical usefulness of epidural spinal electrical stimulation in the treatment of patients with severe angina pectoris.

Patients and methods

PATIENTS

Ten patients (two women and eight men, aged 51–74 years) were selected from the medical outpatient clinic at Östra Hospital, Gothenburg. Table 1 summarises the patient characteristics. All patients had severe angina pectoris (New York Heart Association functional class III or IV). No patients had obstructive or restrictive pulmonary disease, intermittent claudication, valve disease, or had had a myocardial infarction within the last six months. All patients had been considered for bypass surgery: four patients had had the operation, two were current candidates for surgery, and four patients were not considered suitable for operation. All patients except two had had a myocardial infarction. The antianginal medication that they were taking at entry to the study was regarded as optimal and treatment was not changed during the study. The patients were told not to smoke or take short acting nitrates for at least two hours before the exercise tests. All patients had been treated with transcutaneous electrical nerve stimulation which had to be stopped because of skin irritation (in seven patients) and/or because the treatment markedly restricted the patient's normally high physical activity (six patients).

The patients were fully informed about the study before entering it. All patients gave their verbal consent to inclusion in the trial. The trial was approved by the University of Gothenburg ethical review committee.

SURGICAL TECHNIQUE AND STIMULATION EQUIPMENT

The stimulation equipment was implanted in the operating theatre by a sterile technique. The patient was placed on an x ray translucent table. The oper-

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Table 1 *Patient characteristics*

Case No	*Age (yr)*	*Sex*	*Duration of angina (yr)*	*Previous infarction*	*Relative heart volume (ml/m^2 body surface)*	*Lactate production during atrial pacing*	*Antianginal treatment*	*Other treatment*	*Bypass surgery*
1	72	M	10	+	850	+	SAN, LAN, BB	Digitalis, diuretics	Not suitable
2	61	M	9	+	400	+	SAN, LAN, BB, CA	Digitalis, diuretics	Yes
3	51	F	2	–	370	+	SAN, LAN, BB	—	Current candidate
4	60	M	14	+	420	+	SAN, LAN, BB	Digitalis, diuretics	Yes
5	72	M	8	+	430	+	SAN, LAN, BB, CA	—	Not suitable
6	72	M	10	+	720	Not performed	SAN, LAN, BB	Digitalis, diuretics	Not suitable
7	66	M	11	+	420	+	SAN, LAN, BB	—	Yes
8	64	M	9	+	410	Not performed	SAN, LAN	—	Yes
9	61	F	7	–	390	Not performed	SAN, LAN, BB	—	Current candidate
10	63	M	14	+	480	Not perfomed	SAN, LAN, BB, CA	—	Not suitable

SAN, short acting nitrates; LAN, long acting nitrates, BB, β blockers; CA, calcium antagonists

ation was performed under local anaesthesia to allow the patient to answer questions from the surgeon during the preoperative test stimulation. The electrode was positioned so that the patient felt a prickling sensation in the region of anginal pain. The ideal position is when the stimulation produces a prickling sensation starting in the precordial area and spreading into the arms as the strength of the current is increased.

The skin incision was made in the midline in the midthoracic region. The epidural space was punctured at the level of T6. A Touhy-type needle was advanced in the midline through the interspaces into the epidural space, which was identified by the loss of resistance method. The stylet of the electrode was bent 20° 10 mm from the distal end to make it easier to manipulate the electrode in the epidural space. The electrode tip was placed in the midline or a few millimetres to the left at the level of T1–T2. The distal end of the intraspinal electrode is sigma shaped to prevent migration. The electrode was firmly sutured to the fascia for the same reason. Unipolar stimulation was used. The pulse generator was placed in a subcutaneous pouch below the left costal arch. An extension lead was tunnelled subcutaneously to the midline incision and connected to the electrode. The pulse generator was telemetrically programmed. We used a commercially available electrical device (Mectronic., Minneapolis, MN, USA). The pulse width was 210 µs, frequency 85 Hz, and an appropriate amplitude was used to produce for comfortable paraesthesia (usually 3–6 V). The pulse generator is turned on or off by a quick touch with an external magnet on the skin over the pulse generator.

DESIGN OF THE STUDY AND EFFECT EVALUATION

The study consisted of three parts:

A run in period (one to two weeks) to standardise the exercise test for each patient and to confirm that the patients were suitable candidates. Three or four tests were performed.

A treatment period (two weeks) when the individually standardised exercise tests were performed. Each patient performed four tests with stimulation and four without, in alternate order.

A post-treatment period (two days) to measure the patient's working capacity after the study.

After the run in period, the stimulator was implanted (see below) and the patients then had a one week postoperative convalescence before the treatment period started.

The following variables were used to assess the effect of epidural spinal electrical stimulation: (*a*) Pulse rate, blood pressure, and the product pulse rate × blood pressure before, during, and after exercise; (*b*) maximal total work during exercise; (*c*) estimated anginal pain and dyspnoea score during and after exercise; (*d*) ST changes during and after exercise; (*e*) the time until the occurrence of angina during exercise tests (time to angina) and recovery time after maximal total work until the pain disappeared, (*f*) the reason for stopping the exercise test. The electrocardiographic characteristics of the patients were analysed with a Marquette CASE 1 electrocardiogram apparatus (Marquette Electronics, Milwaukee, WI, USA), which was used for continuous monitoring throughout the exercise session. This device eliminates noise and baseline variations in the electrocardiogram and can measure ST segment displacement with an accuracy of 0·1 mm (0·01 mV), which is five times better than can be done by ocular assessment. The systolic blood pressure was measured by a sphygmomanometer.

Exercise tests were always performed both in the morning and in the afternoon. During the treatment period, the order of the daily runs with and without stimulation was alternated randomly. An electrically braked bicycle ergometer (Siemens-Elema) was used and the test was always performed in the same room, at the same temperature, and at the same time of the day. The workload was increased every minute. An increase of 5 or 10 W was used for each patient. The starting load was chosen so that the patient reached his maximum total work after 5–9 minutes. The total work was calculated as the sum of the load-time products for each minute. During the exercise tests with stimulation, the stimulator was switched off for the last 15 seconds of each minute to avoid the stimulator interfering with the electrocardiogram.

Chest pain and dyspnoea were rated according to a common scale ranging from 0 to 5: where 0 represents no discomfort, 3 discomfort equivalent to that which normally stopped the patient's activities, 4 severe, and 5 maximum discomfort. To reach maximum discomfort, the patients were urged to continue their exercise to levels producing either pain or dyspnoea of grade 4 or 5. When the maximal workload was reached, the degree of anginal pain and dyspnoea was recorded each minute until angina score was 0 (recovery time).

To evaluate the statistical significance of the effects of epidural spinal electrical stimulation, the data were grouped in three ways: (*a*) Run in values were compared with those recorded without epidural spinal electrical stimulation in the treatment period, (*b*) values recorded without epidural spinal electrical stimulation were compared with those during epidural spinal electrical stimulation; and (*c*) run in values were compared with post-treatment values.

Data were compared by Fisher's test for paired comparisons.[3] The test is non-parametric. Two-sided tests were used.

Results

No complications or adverse effects were seen during the exercise tests and all 10 patients completed the study. In one patient, the tip of the electrode was initially placed too high and in another patient the electrode migrated. These two patients were easily reoperated on and electrical stimulation was later successful.

Table 2 shows the heart rate, mean systolic blood pressure, and product of heart rate and blood pressure at maximal work, and table 3 shows the same variables at maximal comparable work. Maximal comparable work is defined as the lowest individual maximal work that a patient reached in the series of tests and thus represents the highest workload that can be used for a comparison study. There were no differences between the group treated with epidural spinal electrical stimulation and the untreated groups for data in table 4.

Time to angina was shorter during the post-treatment period than during the run in ($p < 0.05$, table 4). No further statistically significant effects were seen when run in data were compared either with data recorded without epidural spinal electrical stimulation or with post-treatment data.

The following differences between values on and off epidural spinal electrical stimulation were statistically significant: an increase in maximal work capacity ($p < 0.01$, table 5), a decrease in the magnitude of ST segment depression at the highest comparable workload ($p < 0.01$, table 6), an increase in

Table 2 *Mean systolic blood pressure (SBP), mean heart rate (HR), and mean product of systolic blood pressure and heart rate at maximal work*

				Treatment period								
	Run in			*Without ESES*			*With ESES*			*Post-treatment*		
Case No	*HR*	*SBP*	*HR × SBP*	*HR*	*SBP*	*HR × SBP*	*HR*	*SBP*	*HR × SBP*	*HR*	*SBP*	*HR × SBP*
1	106	130	13750	113	123	13600	105	117	12243	103	121	12643
2	67	127	8537	77	120	9230	79	137	10817	73	135	9750
3	128	150	19197	125	158	19793	150	176	25925	132	165	21695
4	97	155	15078	94	169	15885	102	155	15739	90	178	15968
5	85	165	14082	95	177	16683	89	167	14781	86	165	14190
6	126	220	27720	115	224	25575	118	224	25908	118	120	25960
7	97	148	14385	98	146	14244	109	143	15565	96	145	13950
8	134	207	27707	132	201	26631	141	194	27225	139	195	27105
9	124	217	26643	114	223	25380	124	203	25196	109	210	22785
10	105	170	17793	106	184	19501	109	175	18820	103	190	19750
Mean	107	169	18469	107	173	18652	113	169	19221	105	172	18361
SD	21	34	6699	16	37	5813	22	33	6273	21	32	5923

ESES, epidural spinal electrical stimulation.

Table 3 *Mean systolic blood pressure (SBP), mean heart rate (HR), and mean product of systolic blood pressure and heart rate at maximal comparable work*

				Treatment period								
	Run in			*Without ESES*			*With ESES*			*Post-treatment*		
Case No	*HR*	*SBP*	*HR × SBP*	*HR*	*SBP*	*HR × SBP*	*HR*	*SBP*	*HR × SBP*	*HR*	*SBP*	*HR × SBP*
1	106	130	13750	110	123	13600	103	127	13087	105	129	13229
2	66	127	8407	74	116	8562	69	127	8865	67	130	8850
3	122	145	17755	117	155	18313	128	169	21649	114	158	17878
4	93	163	15070	91	171	15495	97	161	15609	89	178	15620
5	84	152	12815	95	177	16683	92	165	15207	84	165	13860
6	129	217	27993	111	219	24229	111	215	23814	112	220	24530
7	90	145	13532	92	146	13436	103	143	14793	94	145	13625
8	128	203	25983	130	201	26031	130	193	25019	133	195	25935
9	116	215	24912	109	216	23796	110	196	21723	104	200	20700
10	103	170	17425	206	284	19501	109	170	17970	103	190	19570
Mean	104	167	17764	104	171	17965	105	167	17774	100	171	17350
SD	21	34	6470	16	36	5543	18	29	5176	18	31	5428

See table 2 for abbreviations.

Table 4 *Mean time to angina (min), mean recovery time (min), and reason for interrupting the test*

				Treatment period								
	Run in			*Without ESES*			*With ESES*			*Post-treatment*		
Case No	*Time to angina*	*Recovery time*	*Reason to stop*	*Time to angina*	*Recovery time*	*Reason to stop*	*Time to angina*	*Recovery time*	*Reason to stop*	*Time to angina*	*Recovery time*	*Reason to stop*
1	2	15·5	Angina	1	12	Angina	2·6	9	Dyspnoea	2·5	13	Angina
2	0·7	7·7	Angina, dyspnoea	0·5	7·3	Angina, dyspnoea	7	1·5	Dyspnoea	1·0	7	Angina, dyspnoea
3	1	1·3	Angina, dyspnoea	3·8	1	Angina, dyspnoea	6·6	0·3	Dyspnoea	4·5	0·5	Angina, dyspnoea
4	1	9·8	Angina, dyspnoea	2·5	5	Angina, dyspnoea	7	1	Dyspnoea	4	5·5	Dyspnoea, angina
5	3·3	1	Dyspnoea	5	1	Dyspnoea	7·3	0	Dyspnoea	6	1	Dyspnoea
6	2	4·7	Angina	3·2	5	Angina	8·8	0	Dyspnoea	3	5	Angina
7	3·3	3·3	Angina	3·0	3·0	Angina, dyspnoea	5·5	2·8	Dyspnoea	3·0	3·5	Angina
8	1·7	3·7	Angina	1·8	3·0	Angina, dyspnoea	8	0	Dyspnoea	2·0	2·5	Angina, dyspnoea
9	2	2·3	Angina	2·3	3	Angina	3·8	1·5	Dyspnoea	2	3·5	Angina
10	1·0	3·0	Angina	1·3	3·3	Angina	3	1·3	Dyspnoea	2·0	3·5	Angina
Mean	1·8	5·2		2·4	4·4		6·0*	1·7*		3·0†	4·5	
SD	0·9	4·5		1·4	3·3		2·2	2·7		1·5	3·6	

*$p < 0{\cdot}01$ for comparison of values with epidural spinal electrical stimulation and without epidural spinal electrical stimulation;
†$p < 0{\cdot}05$ for comparison of run-in and post-treatment values.

Table 5 *Mean exercise tolerance (expressed in W.min)*

		Treatment period		
Case No	*Run-in*	*Without ESES*	*With ESES*	*Post-treatment*
1	200	218	255	255
2	295	319	650	393
3	523	593	713	680
4	423	386	460	385
5	362	362	412	385
6	362	385	520	385
7	523	516	590	505
8	967	830	1083	910
9	523	598	780	620
10	303	330	356	330
Mean	448	453	581*	483
SD	213	180	240	199

*$p < 0{\cdot}01$ for comparison of values with epidural spinal electrical stimulation (ESES) and without epidural spinal electrical stimulation

time to angina and a decrease in recovery time ($p < 0{\cdot}01$ for both, table 4).

The reasons for stopping the exercise were different during epidural spinal electrical stimulation when nine patients stopped because of dyspnoea and one patient stopped because of a combination of angina and dyspnoea.

Discussion

The results of the study accord with the short term effects of transcutaneous electrical nerve stimulation on angina pectoris.[1] Thus epidural spinal electrical stimulation reduced chest pain, increased working capacity, reduced ST segment depression, increased time to angina, and reduced the recovery time. The

Table 6 *Mean ST segment depression (mm) at highest comparable workload and at maximal workload*

			Treatment period					
	Run in		*Without ESES*		*With ESES*		*Post-treatment*	
Case No	*Comparable workload*	*Maximal workload*	*Comparable workload*	*Maximal workload*	*Comparable workload*	*Maximal workload*	*Comparable workload*	*Maximal workload*
1	−0·6	−0·6	−0·7	−0·7	−0·7	−0·7	−0·7	−0·7
2	−0·1	−0·1	−0·1	−0·1	−0·1	−0·1	−0·2	−0·2
3	−2·0	−1·9	−1·8	−1·9	−1·0	−1·8	−1·9	−2·3
4	−2·4	−2·7	−3·0	−3·3	−2·2	−2·7	−2·6	−2·6
5	−0·7	−0·9	−0·2	−0·2	+0·3	+0·2	−0·1	−0·1
6	−3·8	−3·8	−3·4	−3·5	−2·5	−3·0	−4·0	−4·3
7	−2·0	−2·1	−1·8	−2·1	−1·4	−1·8	−2·0	−2·3
8	−2·3	−3·1	−2·4	−2·6	−1·8	−3·1	−2·8	−3·1
9	−2·7	−3·1	−3·1	−3·6	−1·8	−3·2	−2·6	−3·6
10	−2·6	−2·6	−2·6	−2·6	−1·8	−1·8	−2·7	−2·7
Mean	−1·9	−2·1	−1·9	−2·1	−1·3*	−1·8	−2·0	−2·2
SD	1·1	1·2	1·2	1·3	0·9	1·3	1·3	1·4

*$p < 0.01$ for comparison of values with epidural spinal electrical stimulation (ESES) and without epidural spinal electrical stimulation at comparable workload.

patients remained on optimal antianginal treatment during the study. These effects are additional to those produced by conventional medical treatment of angina. In a previous study, the pain relieving effects of transcutaneous electrical nerve stimulation were investigated in patients with severe angina pectoris in pacing induced angina.[4] The treatment had beneficial effects; it increased tolerance to pacing, improved lactate metabolism, and produced less ST segment depression.

The symptoms of angina pectoris are subject to various placebo influences and there is reason to believe that surgical procedures are especially likely to produce such effects,[5 6] It is not possible to design a blind study of epidural spinal electrical stimulation since there is no acceptable placebo equivalent to the sensation of stimulation. Placebo effects must therefore be expected in this study.

"Soft" indices, such as time to angina, recovery time, and working capacity, are especially subject to the influence of placebo effects while "hard" data like the rate-pressure product and ST segment depression are probably less influenced by such effects. Because these variables were altered by electrical stimulation it seems reasonable to assume that physiological mechanisms other than the placebo effect are of importance in this study.

Previous studies have demonstrated that changes in the rate-pressure product are good predictors of myocardial oxygen consumption in patients with angina pectoris.[7] At maximal comparable workload, the rate-pressure product did not differ between the patients treated with electrical stimulation and controls. Thus the effects of epidural spinal electrical stimulation on exercise induced angina pectoris seem not to be correlated to any changes in myocardial oxygen demand.

We believe that transcutaneous electrical nerve stimulation and epidural spinal electrical stimulation reduce some aspects of sympathetic activity. This explanation of their beneficial effects on angina pectoris is supported by the fact that treatment with transcutaneous electrical nerve stimulation reduced arterial concentrations of noradrenaline and adrenaline during atrial pacing.[8] In two patients there was also an increase of dynorphin during transcutaneous electrical nerve stimulation suggesting that the endogenous opoid systems were affected.

In conclusion, the results of the study indicate that the antianginal effect of epidural spinal electrical stimulation is associated with decreased myocardial ischaemia, as shown by the reduction of ST segment depression. The effect seems to be additional to that of pharmacological treatment. The treatment was especially suitable for patients who had to withdraw from treatment with transcutaneous electrical nerve stimulation because of skin irritation and/or because the stimulation restricted their normally high physical activity.

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Infective endocarditis: incidence and mortality in the North East Thames Region

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SUMMARY A survey of infective endocarditis in the North East Thames Regional Health Authority was carried out over a period of 30 months from 1982 to 1984. The incidence, clinical characteristics, and in-hospital mortality were studied. Important causes of endocarditis were dental treatment, the presence of dental disease, drug abuse, and cytoscopy. The omission or incorrect administration of antibiotic prophylaxis in patients with valve disease was noted, but failure of correctly prescribed antibiotic prophylaxis was not recorded. Adverse prognostic features were increased age, prosthetic valve infection, Gram negative or staphylococcal infections, and aortic valve involvement. In contrast, mortality was lower in patients with mitral valve prolapse, ventricular septal defect, and streptococcus viridans infection. Deaths were usually attributable to irreversible complications present at the time of diagnosis. Vegetations were detected on the echocardiogram in half of those studied and mortality was higher in those with vegetations than without. Operation for native valve infection was associated with a low mortality and it is likely that the overall mortality for infective endocarditis has been improved by surgical intervention.

Since 1909[1] infective endocarditis has been the subject of several important surveys. The most recent was from the Medical Services Study Group of the Royal College of Physicians and was completed in 1982.[2–4] Earlier reports often came from referral centres and patients were enrolled for up to 10 years so that sufficiently large study groups could be accumulated by single institutions.[5–8] Many patients with infective endocarditis are now managed in district general hospitals whereas in these earlier studies more complex cases sent to referral centres were over-represented. Published data on incidence, mortality, and clinical features are unlikely to reflect accurately the impact of current preventive, diagnostic, and therapeutic interventions.

We set out to document the current features of infective endocarditis within the North East Thames regional population, aiming to obtain accurate incidence and mortality figures. This approach differed from that of the Medical Services Study Group[2–4] which reported from the whole of the United Kingdom with a relatively low sampling rate and consequently encountered difficulties in assessing incidence and mortality.[9]

Patients and methods

All physicians in the North East Thames Region were asked to register cases of infective endocarditis at the time of diagnosis and to complete a questionnaire after the discharge or death of the patient. A nominated physician in each health district acted as a coordinator to encourage case reports from all physicians, geriatricians, surgeons, and pathologists.

Because we expected that case reporting might be incomplete we also actively sought cases. The Regional Hospitals Activity Analysis centre provided details of all cases coded as endocarditis on death or discharge. These were followed up and the consultants responsible were asked to complete the questionnaire on these cases. Five cases diagnosed at necropsy were similarly followed up to obtain clinical data. The survey lasted 30 months (June 1982 to November 1984). Patients registered more than once (that is intraregional transfer or multiple admissions) were counted as a single case.

Reports were received from most of the hospitals in the region and in most instances the case notes were reviewed in the study centre where the ques-

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tionnaire was completed. The topics covered in the questionnaire included causative events, antibiotic prophylaxis, clinical and microbiological features, echocardiography, and the outcome of medical or surgical treatment.

The 1981 census records and more recent census monitors[10] gave mid-year population figures for the North East Thames Region adjusted for births, deaths, and migration. These figures were used to estimate incidence.

Results

INCIDENCE

The regional hospital activity analysis statistics showed 197 cases coded as infective endocarditis during the survey period. We studied 173 (88%) of these; the remaining 24 case records were not made available to the survey despite repeated attempts to include them. We found that 18 cases were incorrectly coded. A further 20 cases registered through the District coordinators had not been coded by the hospital activity analysis at the end of the survey period. There were a further 10 cases from the London Chest Hospital; these are not reported through the regional hospital activity analysis system. In total 185 cases of infective endocarditis were included in this survey which lasted 30 months.

The regional population was 3 375 million; therefore the incidence per annum of patients *treated* for infective endocarditis was 23 per million. There were five extra-regional patients and when they were excluded the estimate of incidence was marginally reduced. If all cases not made available are assumed to be accurately coded then the *maximum* estimate of incidence would be 25 cases per million. Extrapolation to the whole of the United Kingdom gives an annual incidence of 1150–1300 cases per year.

MORTALITY

Overall mortality was 21% (39 of 185 cases) but mortality in the different subgroups varied considerably. Infection associated with native valve or congenital heart disease had a mortality of 7% (2/29) for those coming to operation and 19% (27/137) for those treated medically. Prosthetic valve infection had a mortality of 53% (10/19).

Increased age adversely influenced outcome with a 34% mortality (28/82) among patients aged $\geqslant 60$ years compared with 9·5% mortality (10/96) in those < 60 years. The mean (SD) age for the whole group was 54·5 (18) years and the mean age of those who died was 63·0 (15) years.

CAUSE OF DEATH

Each of the 39 deaths was reviewed in detail to establish the major cause of death and whether different management might have altered the outcome.

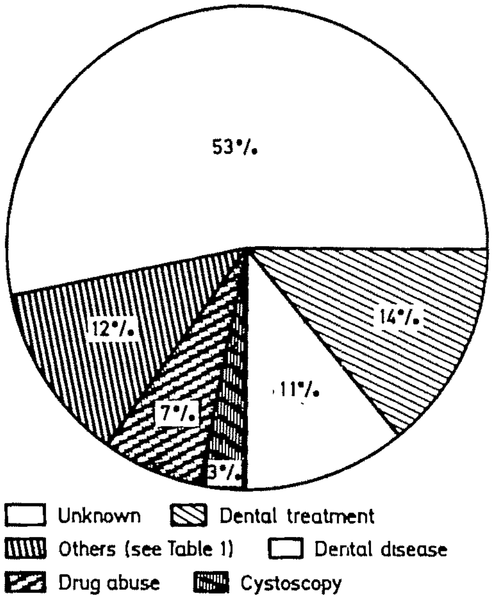

Fig 1 *Source of infection*

It was clear that in the majority of these cases major complications were present, often being the cause of admission to hospital. The major causes of death were heart failure (10), uncontrolled infection (9), stroke (8), sudden death (6), renal failure (2), pancreatitis (1), and unknown in two. When the information on the cases was examined in greater detail there was usually a combination of complications that had contributed considerably to the death. This is shown by the fact that six of the nine patients with uncontrolled infection had advanced renal failure and two others had systemic embolisation before death. The majority of deaths appeared to be unavoidable but in three patients with heart failure operation could have been considered and three might have benefited from earlier in-hospital diagnosis.

Table 1 *Unusual sources of infective endocarditis in 23 cases*

Source	*No*	*Source*	*No*
Colonic surgery	2	Cardiac pacing	1
Eczema	2	Chiropody	1
Haemodialysis	2	Coarctation repair	1
Intravenous cannula	2	Labour	1
Prostatism	2	Obstructive jaundice	1
Septic arthritis	2	Sinusitis	1
Skin abscess	2	Gland infection	1
Cardiac catheter	1	Urethral surgery	1

SOURCES OF INFECTION LEADING TO INFECTIVE ENDOCARDITIS (FIG 1, TABLE 1)

No source of infection was identified in over half the cases. The most frequent single cause for infective endocarditis was dental treatment within three months of symptoms; this occurred in 26 (14%) patients. In 21 (11%) patients untreated dental disease was present and was thought to be the source of infection. Thus dental treatment or disease was implicated in 25% of all cases.

Drug abuse (6·5%) was an important cause of infective endocarditis, with tricuspid valve infection occurring in 11 of the 12 cases reported. Although poor compliance tended to reduce the length of treatment in these patients the early in-hospital mortality was only 8% (one death in 12 patients).

Cytoscopy or prostatism preceded *Streptococcus faecalis* (6 patients) or *Str enterococcus* (1 patient) infection. The variety of other causes (table 1) indicates the many situations in which bacteraemia (and hence endocarditis) may occur.

ANTIBIOTIC PROPHYLAXIS

In seven patients it was suggested that prophylactic antibiotics had been given before endocarditis developed; on close examination none was established as a failure of antibiotic prophylaxis. One patient received appropriate antibiotics but only after dental treatment had been completed. In three patients appropriate antibiotic cover had been given but clinical and microbiological data indicated that the subsequent infective endocarditis was unrelated to the procedure for which the antibiotics had been given. In one case which occurred after dental treatment the patient had not received adequate doses of erythromycin.[11] One case of streptococcus viridans endocarditis that occurred six weeks after labour is of uncertain origin. An intramuscular dose of amoxycillin was given two hours before the start of the second stage of labour and plasma concentrations would have been low at the time of greatest risk of bacteraemia. In another patient who had had dental extraction correctly covered with amoxycillin a year earlier, streptococcus viridans endocarditis was attributed to the presence of further dental sepsis.

Table 2 *Symptoms of infective endocarditis*

Sign or symptom	%
Fever	79
Malaise	79
Weight loss	39
Dyspnoea	42
Pyrexia	84
Pallor	47
Splinter haemorrhage	26
Splenomegaly	21
Clubbing	9
Ocular emboli	6

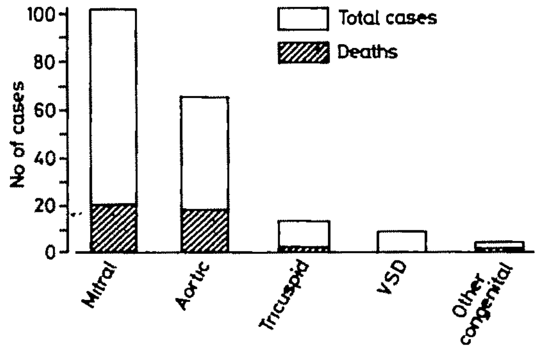

Fig 2 *Site of infection.*

Six patients had not been given antibiotic prophylaxis despite recognised cardiac indications for its use. Two patients were not given antibiotics because it was thought unnecessary for dental scaling. Another had dental treatment without cover, but no reason was given for this omission. Excision of an abscess (two cases) and chiropody (one case) were reported to precede staphylococcal infection and no antibiotics had been given before these procedures in patients known to have prosthetic cardiac valves.

CLINICAL FEATURES

The symptoms and signs at presentation (table 2) reflect the recognised features of infective endocarditis. The mean (SD) duration of symptoms was 6·2 (5·5) weeks but the symptomatic period before diagnosis was shorter among those patients who died than in those who survived (4·2 (3·3) weeks *vs* 6·8 (5·9) weeks). This was true for patients treated medically or surgically. Staphylococcal and Gram negative infections were associated with a short duration of symptoms (3·0 (3·2) weeks) and were more frequently found in the patients who died. For each organism there was no difference in the symptomatic period before diagnosis in survivors and nonsurvivors.

Endocarditis was more frequent on the mitral valve than on the aortic valve (55% *vs* 35%) and carried a lower mortality (21% *vs* 28%) (fig 2).

Mitral valve prolapse (19%) and rheumatic heart disease (18%) were the most frequently recognised valvar abnormalities but in many patients (29%) no underlying cardiac abnormality was recognised. Mortality associated with infection on rheumatic valves (24%) and bicuspid aortic valves (28%) was much higher than that for mitral prolapse (6%). Mortality was high (53%) in patients with prosthetic

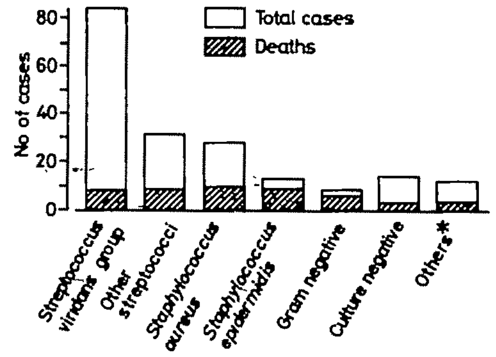

Fig 3 *Microbiological results.*
**Haemophilus parainfluenzae (3), Lactobaccillus (2), Mixed culture (4), diphtheroid sp. (1), Q fever (2).*

valve endocarditis whereas infective endocarditis in patients with congential heart disease had a low mortality (7%).

MICROBIOLOGICAL RESULTS (FIG 3)

Our data show the continuing importance of streptococcal infection, with 113 (61%) cases recorded. Viridans group streptococci caused 45% of cases (83 patients) and only 38% (31 patients) of these were associated with dental treatment or disease. The mortality for viridans infection was 7% while infection with the other streptococci carried a mortality of 20%. Staphylococcal infection occurred in 21% (39 cases), the mortality being greater for *Staphylococcus epidermidis* (67%, eight out of 12) than *Staphylococcus aureus* (30%, eight of 27 cases). All five patients with *Staph epidermidis* infection on a prosthetic valve died.

Six of the seven patients with Gram negative infection died. There were 14 (8%) culture negative cases but all had clinical, surgical, or necropsy features to support the diagnosis of infective endocarditis.

ECHOCARDIOGRAPHY

Echocardiography was performed on 140 (76%) patients in the survey. Vegetations were detected in only 23% (six out of 26 patients) who had M mode studies compared with 49% (55 of 114) when combined M mode and cross sectional echocardiography was performed.

In native valve infection mortality was 13% (8/60) in patients with vegetations on the echocardiogram and 8% (5/64) in those without. In two cases persisting mobile vegetations were taken as an indication for operation, one of these patients having experienced a systemic embolus. Vegetations were identified in only one of 16 patients with prosthetic valve infection.

HAEMATOLOGICAL AND BIOCHEMICAL INVESTIGATIONS

Initial or peak values (mean) for plasma urea and creatinine were high in those patients who subsequently died. The early haemoglobin concentrations and white cell counts were similar in survivors and non-survivors and most patients had values within the normal range. The erythrocyte sedimentation rate varied considerably and in eight patients the initial rate was under 20 mm/h. Microscopic haematuria was detected in 28% (52 cases) and was more common in those who died (41% (16 of 39)) than in the survivors (24% (36 of 146)).

PROSTHETIC VALVE INFECTION

Mortality was high (53%) in the 19 patients with infection on a prosthetic valve. Aortic and mitral valve involvement were equally common and there were five deaths associated with infection at each of these sites. Because the numbers are low no conclusions can be made about the relation between type of prosthesis and outcome, although infection was more common on mechanical (13) than bioprosthetic (6) valves. *Staph epidermidis* infection was more common in patients with prosthetic valves, and all five cases died.

SURGICAL TREATMENT

The results of surgical treatment were good. Eighty two per cent (28 patients) survived and 18% (six patients) died. When those treated for native valve infection are considered separately the mortality is much lower at 7% (2/29) and is better than that recorded for medically treated patients. Since most operations were performed because of acute and severe haemodynamic complications the results can be regarded as encouraging. Surgery for prosthetic valve endocarditis was successful in only one of five patients who had an operation.

Discussion

This is the second large survey of infective endocarditis to be reported from the United Kingdom in the 1980s, the Medical Services Study Group of the Royal College of Physicians in collaboration with the British Cardiac Society having published data on 541 patients.[2-4]

Our study was designed to encompass the whole population of patients with infective endocarditis in the North East Thames Region, without a bias towards those presenting to referral centres, and to permit the estimation of overall incidence and mortality. We found the annual incidence to be 23–25 cases per million and extrapolation of this figure to the whole of the United Kingdom gives a total incidence of 1150–1300 cases. These figures are higher than those from earlier series, but they resemble the incidence reported from a population of 1·8 to 2·0 million around Lyons in France (40–50 cases per year).[12]

The Royal College of Physicians survey reported a relatively low number of cases associated with drug abuse (2%), a relatively high number of prosthetic valve infections (17%), and a low overall mortality (14%), supporting the authors' view that there was a low sampling rate and some sampling bias in the study that prevented accurate estimates of incidence and mortality.[9]

We found the overall mortality to be 21% and this should replace the widely quoted figure of 30% which was based on data from the 1960s and 1970s[5 7 8] when surgical intervention was not widely practised. The number of deaths from infective endocarditis registered in the United Kingdom is approximately 250 cases per year.[9] Based on the mortality rate of 21% from our survey the calculated incidence of infective endocarditis is 1250 cases per year which closely matches our estimated incidence.

We found that a considerable proportion of cases (25%) was related to either dental treatment or the presence of dental disease. Recent investigation of dental causes of endocarditis showed that 103 (19%) of 541 cases were associated with dental procedures or dental sepsis. It was estimated in 1978 that 20–30% of the United Kingdom population had dental or periodental disease[13]; this accords with the amount of dental disease we found in the population with infective endocarditis. An improvement in the dental health of the population should therefore reduce the incidence of infective endocarditis arising because of chronic dental infection. Increased detection of asymptomatic heart valve disease, followed by appropriate advice would allow the population at risk to be better protected, but would prove a formidable logistic exercise. Endocarditis can arise in previously normal hearts and three patients treated surgically in our series were seen to have "normal" valves apart from the damage from vegetations. The value of offering prophylactic antibiotic treatment to all patients over 60 years receiving dental treatment has been examined[2 14 15] but no definitive recommendation has emerged. In our study only 35 of 83 patients with viridans infection were over 60 years and, of these, endocarditis followed dental treatment in only seven. Routine prophylaxis for dental treatment in all subjects over 60 years would therefore offer only limited reduction in the incidence of infective endocarditis in this age group.

There has been considerable interest in the usefulness of antibiotic prophylaxis in patients known to be at risk, and advice on this has been available for some years.[16 17] We found that there were no failures of prophylaxis when the appropriate antibiotic had been given in the correct dose and at the optimum time to cover a particular procedure. Closer analysis of the nine cases of possible prophylaxis failure among 541 cases[3] shows that only three are likely to be true failures of antibiotic prophylaxis for dental treatment. A recent case report gave a further example of a true failure of prophylaxis, but in a complex clinical setting.[18] Our impression is that if only three from a total of over 700 cases of endocarditis are thought to result from true failure of prophylaxis it is reasonable to conclude that there is a high rate of protection obtained when prophylaxis is properly used for the large number of patients for whom it is recommended.

The current advice on antibiotic prophylaxis was simplified and widely published in 1982.[16] In at least eight of our 185 patients and in several examples from the Royal College of Physicians report,[3] antibiotics were not given when they should have been or they were incorrectly prescribed. An alarmingly high rate of ignorance about some aspects of antibiotic prophylaxis for endocarditis was found among physicians, surgeons, dentists, and general practitioners in a recent survey,[19] and cardiologists and others should ensure that both patients and doctors are aware of the oral amoxycillin prophylaxis regimen.

Our findings confirm the continuing importance of streptococci, which accounted for 61% of infections. The incidence of viridans infection (45%) is of the same order as that found in the 1960s and 1970s.[6–8] In our series 15% of cases (28 patients) had infections from organisms normally found in the bowel or genitourinary tract, and a similar incidence was reported by the Royal College of Physicians' survey.[4] We found specific causes for *Strep faecalis* infection in five of 10 cases (cystoscopy three, and prostatic disease two). Among 18 infections with other bowel organisms, only two had a clear cause identified. In both a colostomy had been fashioned, one for carcinoma of the colon and one for carcinoma of the prostate. The high mortality (67%) found with *Staph epidermidis* infections suggests that the traditional view that this organism is not an important pathogen should be altered in the context of infective endocarditis particularly when a prosthetic valve is affected.

The clinical features (table 2) confirm the findings in other series. A short duration of symptoms before diagnosis was a striking feature among those with a higher mortality and this probably relates mainly to the characteristics of the infecting organism in these cases.

Echocardiography is of diagnostic value in infective endocarditis. In this study the rate of detection of vegetations was doubled by the use of combined M mode and cross sectional studies compared with M mode studies alone. The overall sensitivity of echocardiography in detecting vegetations was only 49%. This detection rate has been reported in the past[20] although others have reported a detection rate of up to 73%.[21] This re-emphasises the important point that a normal echocardiogram does not exclude the diagnosis of endocarditis. Clinical and microbiological findings remain the main diagnostic criteria and the role of echocardiography is to confirm the diagnosis. There was a higher mortality in patients in whom vegetations were detected (13% *vs* 8%). Vegetations were imaged echocardiographically in only one of 16 patients with prosthetic valve endocarditis although several who had operation were found to have large vegetations around the valve. This is because of the highly echogenic nature of the prosthesis which makes differentiation of the features of vegetations difficult.

The important contribution of surgical treatment to the management of infective endocarditis is evident from the results reported here and other recent surveys.[6 22-24] We suspect that this is the major reason for the fall in overall mortality from 30% to 21%. Many patients with severe haemodynamic deterioration because of valvar regurgitation had a favourable outcome after operation. The mortality for surgical patients was considerably better than for medical treatment of native valve infection (7% *vs* 19%). This indicates that the haemodynamic consequences of infective endocarditis can be effectively treated by operation whereas other complications (for example, uncontrolled infection, sudden death, stroke) do not necessarily respond so well to the use of antibiotic chemotherapy or other medical interventions. After analysing the case records of the patients who died we believe that most deaths were unavoidable, mainly because serious complications were already established at the time of admission to hospital. It is clear that many of the complications of endocarditis are unresponsive to treatment and therefore prevention of the infection or early diagnosis are the best means of reducing overall mortality.

It is likely that endocarditis will continue to be a major clinical challenge mainly because of the unknown aetiological factors in nearly half the cases, the number of individuals presenting who were not previously known to have cardiac abnormalities, and increasing numbers of patients with prosthetic valves. A reduction of incidence might occur with improvements in the use of antibiotic prophylaxis or in the dental health of the population. Surgical results are good and have contributed to a reduction in mortality to 21%. The mortality figures might have been further improved by earlier diagnosis or operation in six of the 39 patients who died.

We are grateful to our colleagues in the North East Thames Physicians Club for their help and support with this project.

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Protein-losing enteropathy caused by baffle obstruction after Mustard's operation

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SUMMARY Three patients developed protein-losing enteropathy caused by intra-atrial obstruction of the systemic venous return after Mustard's operation. The enteropathy resolved in one case after reoperation and in the others after balloon dilatation of the stenosed caval pathways.

Protein-losing enteropathy may occur as a complication of Mustard's operation. Balloon dilatation of the obstructed baffle is an effective alternative to reoperation.

Obstruction of the systemic venous return is a recognised complication of Mustard's operation. Protein-losing enteropathy has been described in only two patients,[1 2] however, both of whom had reoperation for relief of the enteropathy.

We describe three children who developed protein-losing enteropathy after combined obstruction of the superior and the inferior vena caval pathways after Mustard's operation. One was successfully treated by baffle reconstruction and the other two by balloon dilatation of the obstructed venous channels.

Case reports

CASE 1

A male infant with transposition of the great arteries had a balloon atrial septostomy at 24 hours of age. Three months later, Mustard's operation was performed using a Dacron patch as the intra-atrial baffle. The pulmonary venous atrium was also enlarged using dura mater. After operation mild periorbital oedema developed. Cardiac catheterisation and angiography showed almost total obstruction of the superior vena caval pathway. The oedema regressed spontaneously over three months.

Three years later he presented with recurrence of his facial oedema and was found to have hepatomegaly and ascites.

The serum protein concentration was 38 g/l, albumin 29 g/l, and globulin 9 g/l. The serum concentration of IgG was 1·19 g/l (normal range 4·24–10·5 g/l) but concentrations of IgA and IgM were normal. There was no proteinuria and the liver function tests were normal.

Studies with chromium-51 labelled albumin showed a faecal excretion of 20·2% of the intravenous dose over five days (normal value < 1·5%).

A chest radiograph showed no cardiomegaly. The table shows the haemodynamic data. Angiography showed an occluded superior vena cava (fig 1a) and severe stenosis of the inferior vena cava (fig 1b) with a dilated azygos vein. In addition, a left upper lobe pulmonary vein drained into the systemic venous atrium.

At reoperation, an intense endocardial reaction was found around the Dacron baffle suture line. A single orifice of the left pulmonary veins drained to the systemic venous atrium and the sites of obstruction were confirmed. The inferior caval pathway was partially obstructed by a shelf of tissue adjacent to the coronary sinus. A new intra-atrial baffle was constructed from calf pericardium.

He subsequently made a full recovery and six months later the total serum protein was 61 g/l and albumin was 41 g/l.

CASE 2

A two week old boy with transposition of the great arteries underwent balloon atrial septostomy. At

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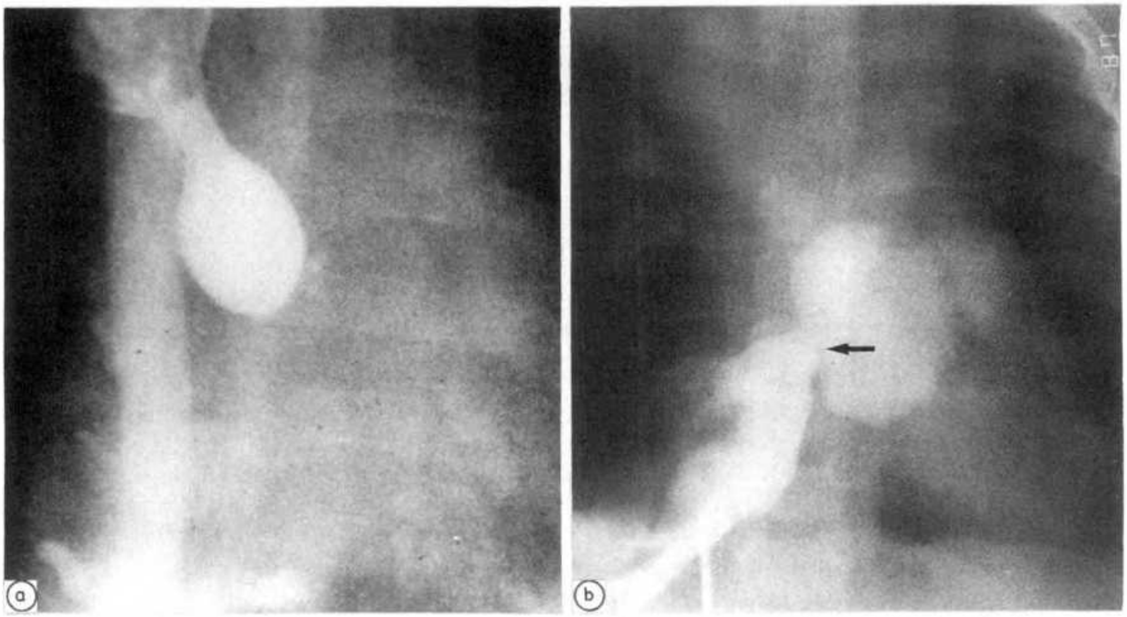

Fig 1 *(a) Angiogram showing complete occlusion of superior caval pathway with a dilated azygos vein. (b) Angiogram showing severe stenosis (arrow) of inferior caval pathway.*

seven months of age Mustard's operation was performed with a baffle constructed from autologous pericardium. His postoperative course was uncomplicated.

Five years later he presented with facial and peripheral oedema, hepatomegaly, and ascites. The total serum protein concentration was 32 g/l, albumin 15 g/l, and globulin 17 g/l. The serum concentration of IgG was 1·14 g/l and the IgA 0·33 g/l (normal range 0·5–2·5 g/l). The IgM and the liver function tests were normal and there was no proteinuria.

At cardiac catheterisation the mean pressures in the superior and inferior vena cavae were 15 mm Hg and 3 mm Hg higher than in the systemic venous atrium. Angiography showed occlusion of the superior vena caval pathway with drainage occurring via a dilated azygos vein to the inferior vena cava. The inferior vena caval pathway was stenosed. The pulmonary venous return was normal.

Table *Haemodynamic data in case 1*

Site	*Saturation (%)*	*Pressure (mm Hg)*
SVC	64	Mean 16
IVC	65	Mean 15
SVA	74	Mean 6
LV	74	36/ 5
MPA	73	34/18
RV	94	85/10
Ao	97	88/48

SVC, superior vena cava; IVC, inferior vena cava; SVA, systemic venous atrium; LV, left ventricle; MPA, main pulmonary artery; RV, right ventricle; Ao, aorta. $Q_p/Q_s = 1{\cdot}5{:}1$ (left to right shunt or systemic to pulmonary shunt).

The stenotic inferior vena caval pathway was dilated firstly with a 12 mm and then with a 20 mm Meditech balloon catheter. The oedema resolved within seven days and the serum concentrations of proteins returned to normal. Four months later his serum albumin was 38 g/l.

CASE 3

A neonate with transposition of the great arteries and a ventricular septal defect had a Blalock-Hanlon septectomy that was followed, at the age of one year, by Mustard's procedure. The ventricular septal defect was closed and an intra-atrial baffle was constructed from Dacron. He remained well for five years but then developed complete heart block and required an epicardial pacemaker. At eleven years of age he returned with an eighteen month history of progressive abdominal swelling. Examination showed generalised oedema, ascites, and hepatomegaly. The total serum protein concentration was 39 g/l, albumin 19 g/l, IgG 3·6 g/l, IgA 0·8 g/l, and IgM 1·3 g/l. Liver function tests and urinalysis were normal.

Bilateral femoral venography showed thrombosis of the inferior vena cava below the renal veins. Cardiac catheterisation was performed by a percutaneous approach via the right subclavian vein.

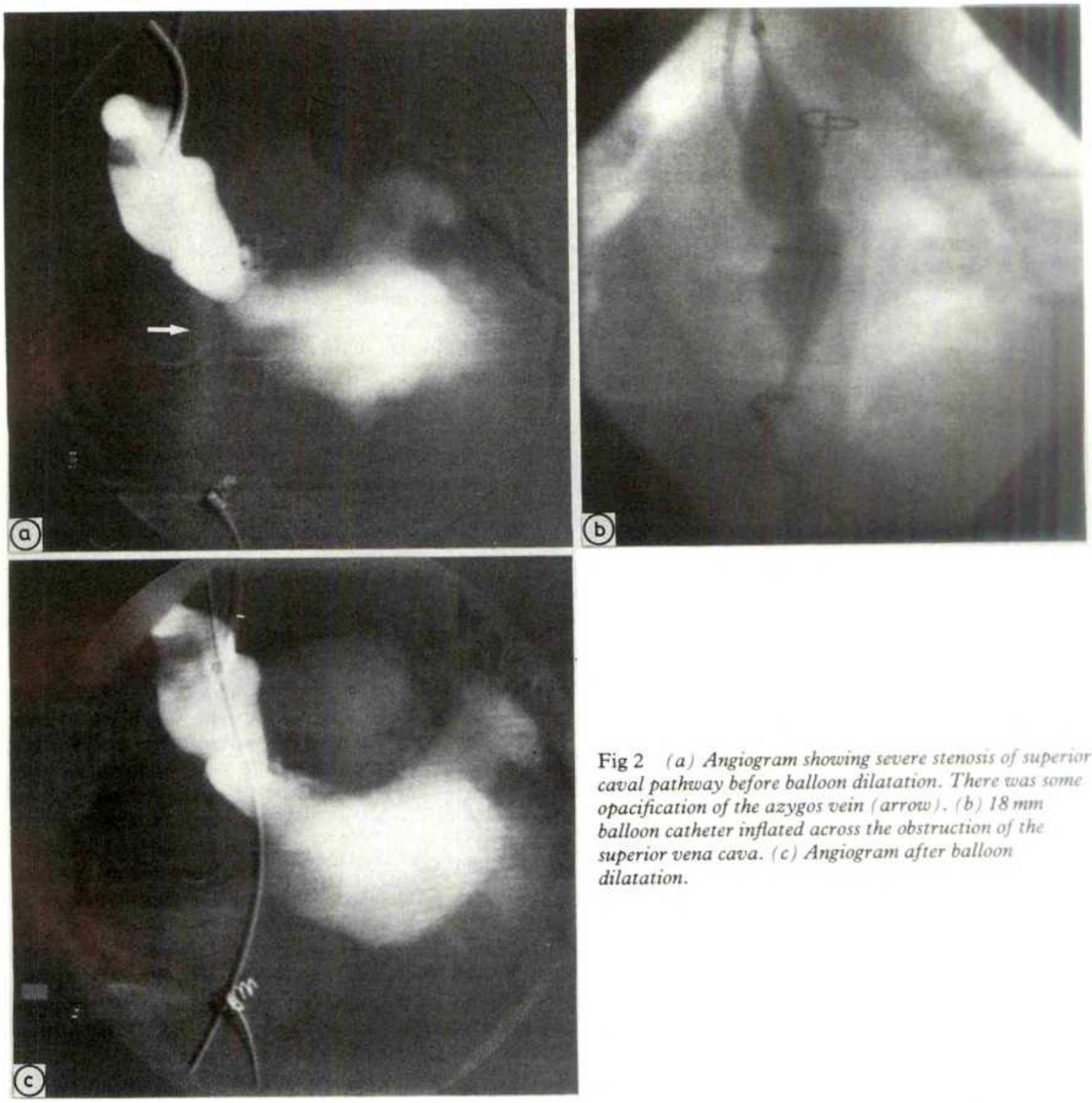

Fig 2 *(a) Angiogram showing severe stenosis of superior caval pathway before balloon dilatation. There was some opacification of the azygos vein (arrow). (b) 18 mm balloon catheter inflated across the obstruction of the superior vena cava. (c) Angiogram after balloon dilatation.*

The pressures in the superior and inferior vena cavae were 22 mm Hg and 15 mm Hg respectively and the left ventricular end diastolic pressure was 6 mm Hg. Angiography showed severe stenosis of superior (fig 2a) and inferior vena caval pathways. The right internal jugular vein was cannulated by an approach anterior to the sternocleidomastoid muscle[3 4] but it proved impossible to advance a balloon catheter over a guide wire positioned in the vein. The internal jugular vein was recannulated by an approach posterior to the sternocleidomastoid muscle.[5 6] An 18 mm Meditech balloon catheter was advanced through the systemic venous atrium and dilatation of the obstructed inferior limb was followed by dilatation of the superior limb (figs 2b and c). The child had a considerable diuresis and there was a weight loss of 3·9 kg. The concentration of serum proteins rose to 53 g/l and albumin to 21 g/l.

Discussion

Protein-losing enteropathy may occur as a complication of various cardiac disorders[7] and after cardiac surgery.[8 9] It was first described after Mustard's operation in 1976[1] and a further case was reported in 1977.[2] Obstruction of the vena caval pathway was the underlying cause of the enteropathy, and baffle reconstruction was required in each case.

The superior vena caval pathway is obstructed in 3–13% of patients after Mustard's operation,[10, 11] but is usually asymptomatic because of an adequate collateral circulation through the azygos venous system. The systemic venous pressure rises if there is coexistent obstruction of return in the inferior vena cava. This increase in pressure impairs drainage of the thoracic duct, the intestinal lymphatic vessels become engorged, and protein is lost from the gastrointestinal tract.[12]

Balloon dilatation via the femoral vein has been successful in relieving obstruction of the vena cava,[13] and this technique was successful in our second case. In our third case, thrombosis of the inferior vena cava precluded this approach. In children it may be difficult or impossible to pass a balloon catheter with a large diameter from an antecubital vein and the subclavian vein approach is potentially hazardous because of difficulty in controlling haemorrhage. Percutaneous catheterisation of the right internal jugular vein from the posterior triangle of the neck is a safe procedure that is particularly suitable for children[6] and obviated the need for reoperation in the third case.

Severe hypoproteinaemia after Mustard's operation may be a consequence of protein-losing enteropathy. If the superior and inferior vena caval pathways are obstructed balloon dilatation should be considered as an alternative to operation.

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Case reports

Myocardial rupture in acute myocardial infarction: urgent management

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SUMMARY Myocardial rupture complicated acute myocardial infarction in a 50 year old man. Resuscitation was started immediately and he was treated with pericardiocentesis and a massive intravascular infusion of fluid. The torn area was plicated with Teflon felt and reinforced with an uninterrupted suture. The postoperative course was uncomplicated.

This report points out the crucial importance of prompt clinical recognition and management of the acute stage of cardiac rupture in acute myocardial infarction.

Rupture of the free wall of the left ventricle complicating acute myocardial infarction is a common cause of in-hospital death. Predisposing factors, clinical presentation, and pathological features have been reported extensively.[1] Despite its prevalence management of myocardial rupture is usually ineffective with only a few successes reported.[2 3]

Case report

A 50 year old man was admitted to the intensive coronary care unit of a community hospital with chest pain in association with weakness and dyspnoea. He had a history of hypertension treated by atenolol 100 mg daily.

On admission the patient was pale and anxious. His blood pressure was 110/80 mm Hg and the pulse rate 100 beats/min. On auscultation of the chest no rales were heard in either lung. The heart sounds were diminished and there was no atrial or ventricular gallop rhythm. No heart murmurs were heard. The peripheral pulses were normal. The electrocardiogram showed an extensive anterior myocardial infarction. The chest *x* ray was normal.

Four hours after arrival at the unit, while he was complaining of severe, crushing pain, the patient suddenly lost consciousness. There was respiratory arrest, pronounced jugular venous distension, and his face and neck became purple. The peripheral pulses were unpalpable. The monitoring lead showed extreme sinus bradycardia and no heart sounds were heard. In the light of the clinical evidence of acute cardiac tamponade, resuscitation was started immediately. Pericardiocentesis was performed and a massive infusion of fluid was started. The pericardial puncture yielded 300 ml of unclotted blood. Progressively, the blood pressure and respiration reappeared. Almost simultaneously the patient recovered consciousness. There was a positive Kusmaull sign and a paradoxical pulse.

A ruptured heart complicating an acute myocardial infarction was diagnosed and the patient was transferred to a centre for cardiovascular surgery and immediately moved to the operating room.

At operation, clots and unclotted blood were removed from the pericardial sac and a hole was identified in the apical area to the left of the left anterior descending coronary artery. This torn area was plicated by Teflon felt and reinforced with uninterrupted sutures. The postoperative course was uncomplicated.

Cross sectional echocardiography and equilibrium radionuclide angiography were performed 10 days after operation. The echocardiogram from a modified apical long axis view (two chamber view)

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showed a clearly delineated, lacerated area, which sharply interrupted the endocardial surface echoes, in the apical segment of the left ventricle free wall. This zone was dyskinetic when compared with the nearly normal function of the posterior left ventricular wall, and it was thin throughout the cardiac cycle, as has previously been described in similar cases.[4]

Angiography was performed after labelling the patient's red blood cells in vivo with 3 mg of intravenous stannous pyrophosphate; twenty minutes later 20 mCi of technetium-99 pertechnetate was injected. Images were recorded in both the anterior and 45° left anterior oblique projections, which best define the interventricular septum. The angiograms showed a global left ventricular ejection fraction of 27%, with akinesis of the anteroseptal wall and a dyskinetic apical segment. The posterolateral wall function was normal.

Discussion

Rupture of the free wall of the left ventricle complicating an acute myocardial infarction may be classified as three clinical types: acute, subacute, and chronic.[5] The acute type is characterised by the rapid development of mechanical arrest at the onset of the rupture of the free wall associated with sinus bradycardia which is followed by a slow atrioventricular junction rhythm. This may be explained, at least in part, by vagal stimulation of afferent nerves originating from the pericardial receptors. The subacute type presents with signs and symptoms resembling cardiogenic shock and the patient can survive a few hours, which permits additional diagnostic procedures (for example echocardiography). The chronic type is characterised by the formation of a pseudoaneurysm. In the subacute type the diagnosis may be completed by rapid echocardiographic demonstration of direct and indirect signs of cardiac rupture, followed by pericardiocentesis, intravascular volume repletion, and surgical repair. Survival in this condition depends on prompt surgical intervention or the rare development of a pseudoaneurysm.

Our patient had the acute type of cardiac rupture with a clinical picture of mechanical cardiac arrest. The immediate pericardiocentesis showed the presence of blood in the pericardial sac, permitting a prompt diagnosis and the introduction of intrapericardial drainage accompanied by massive intravascular fluid repletion. This approach produced a dramatic haemodynamic improvement so that the patient could be transferred to another hospital for urgent cardiac surgery.

This report emphasises the crucial importance of prompt clinical recognition of the acute stage of cardiac rupture associated with acute myocardial infarction. Immediate pericardiocentesis, with no delay for other diagnostic procedures, meant that urgent surgical intervention could be attempted.

Successful repair of ventricular rupture may be followed by long term survival,[6] as it was in our patient (eight months).

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Wolff-Parkinson-White syndrome: inadvertent permanent ablation of the accessory pathway during electrophysiological study

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SUMMARY A case of permanent unintentional ablation of an accessory pathway during electrophysiological study is reported. Possible factors predisposing to such ablation include the location and depth below the endocardium of the accessory pathway.

Ablation of the accessory pathway is an established form of treatment in patients with the pre-excitation syndrome.[1] Conventionally, this is performed at operation but it has more recently been achieved by techniques that use transvenous wires.

Unintentional ablation of the accessory pathway may follow His bundle ablation[2] and may also be a transient phenomenon during electrophysiological study.[3] We report a case of permanent ablation of the accessory pathway that followed the introduction of a recording wire into the coronary sinus.

Case report

An 18 year old man was referred for evaluation of a narrow complex tachycardia that had been refractory to medical treatment. He had initially presented at the age of 12 days with congestive heart failure secondary to paroxysmal tachycardia. He remained symptom free on digoxin until the age of 16 years when tachycardia recurred. Despite treatment with various medications the arrhythmia persisted and he was admitted for electrophysiological study.

Physical examination was normal. Although pre-excitation was absent at times, 12 lead electrocardiograms usually showed the Wolff-Parkinson-White pattern type B (fig 1). At the beginning of electrophysiological study the pre-excitation was apparent but after the placement of the transvenous electrodes delta waves were no longer seen.

Despite pacing from multiple sites no evidence could be found of anterograde or retrograde conduction across an accessory pathway and reentrant arrhythmia could not be induced. Limited electrophysiological studies were repeated on two subsequent occasions and again failed to show any evidence of pre-excitation or tachycardia. Since the initial electrophysiological study five years ago the patient (now 23 years old) has had no tachycardia and no subsequent electrocardiograms have shown evidence of the Wolff-Parkinson-White syndrome (fig 2).

Discussion

Interruption of the accessory pathway either surgically[4 5] or by transvenous wires[1] is now an

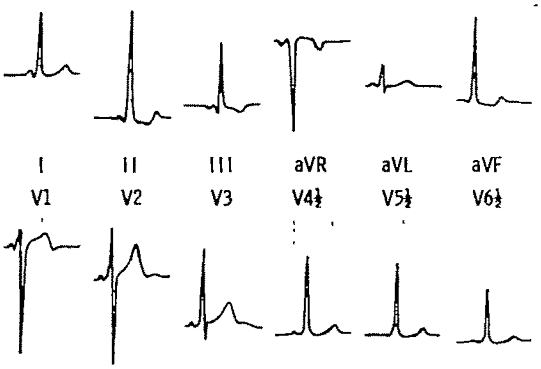

Fig 1 *Twelve lead electrocardiogram recorded before electrophysiological study and showing Wolff-Parkinson-White syndrome type B.*

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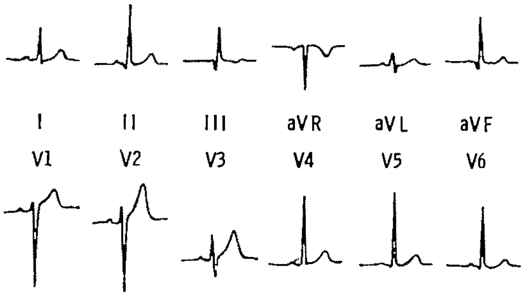

Fig 2 *Twelve lead electrocardiogram recorded after electrophysiological study. The pattern of pre-excitation has disappeared.*

established treatment in the Wolff-Parkinson-White syndrome. Though transient disturbances of accessory pathway function have been reported,[3] we are unaware of permanent destruction of a bypass tract during electrophysiological study produced by manipulation of the wire alone.

Interruption of conduction by an accessory pathway in this manner will depend on several factors, including the site of the accessory pathway, its dimensions, and its depth below the endocardium, as well as the vigour with which the wire is being manipulated. The ease with which destruction occurred in this case, with gentle movement of the wire, suggests that the site or depth below the endocardium or both may have rendered the pathway susceptible to minor trauma. We cannot distinguish whether the pathway was in the mouth of the coronary sinus or just beneath the endocardium, over the atrioventricular node itself.

Although there are some reports that deal with the size of bypass tracts,[6 7] the depth of accessory pathways below the endocardium has received scant attention, though Lev *et al* reported a right-sided subendocardial accessory pathway[8] and this has been considered important in determining the type of surgical approach.[9]

The depth below the endocardium of these pathways may also determine their susceptibility to attempts at intracardiac electrical ablation; this may explain the relative ease with which some ablations are performed while others prove difficult. Furthermore, vascular anomalies of the coronary sinus may also be associated with Wolff-Parkinson-White syndromes and possible transvenous destruction of these might also have accounted for the disappearance of pre-excitation.[9]

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Chronic constrictive pericarditis caused by self-mutilation with sewing needles

A case report and review of published reports

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SUMMARY A 34 year old woman with a history of self-mutilation developed severe constrictive pericarditis with sterile, calcified intrapericardial abscess cavities as a result of inserting sewing needles into her chest seven years previously. After pericardiectomy she made a good recovery.

In peacetime needles are the most common foreign bodies found in the pericardial sac, whereas bullets and shrapnel become more common in times of war.[1] In the nineteenth century it became fashionable to attempt suicide by driving a long pin, needle, or skewer into the heart. Admiral Villineuve who commanded the French fleet at Trafalgar was taken prisoner by the English. After his release he returned to Rennes from where he sent a message to Napoleon announcing his return to French soil. Suffering from guilt and depression, and failing to receive a reply from Napoleon, whom he knew to be more than a little displeased, he killed himself by driving a long needle six times into his heart.

In 1868 Fischer described 452 patients wounded in the heart or great vessels and showed that such wounds were not always fatal.[2] He recorded 319 penetrating wounds, mainly stab and gunshot, but 44 were puncture wounds. Of these, 28 were caused by various types of needles and only 10 patients survived the initial injury.

In 1899 Loison reported a further series of 61 penetrating injuries; in 23 cases these were caused by needles. Some of these patients were symptomless while others died suddenly for unknown reasons.[3] Fourteen (61%) died; eight of haemorrhage with tamponade, and one of infection. In five the cause of death was not known.

The first patient to survive the attempted removal of a needle from the heart was reported by Gérard in 1835 (case number 37 of Fischer's series). Gérard saw a schoolboy who had pushed a knitting needle through his breastbone. The boy's companion pulled out what he believed to be the intact needle. Over the next six years the boy developed pain in the cardiac region at night and subsequently died of pneumonia. At necropsy a long metal splinter was found in the wall of the right ventricle. The splinter extended into the ventricular septum and was covered with fibrosis and organised thrombus.

In Loison's series, needles were removed successfully from seven of the nine patients who survived.

It seems surprising that at the same time that needles became a fashionable suicide weapon, a Mr Foot reported to the Royal Academy of Medicine in Ireland that, "in Warsaw the latest treatment for cholera was puncturing the heart with a needle to stir up vitality."[4]

The number of pericardial needle injuries caused by self-mutilation declined this century, with only a few cases being reported in English language publications,[5-11] plus one caused by a straightened safety pin.[12] In two cases needles were introduced into the pericardium during medical treatment—intracardiac injection of adrenaline[13] and a posterior pleural aspiration.[14]

There are 12 reports of the incidental finding at necropsy of needles embedded in the heart.[14 15] These may have been the result of unrecognised self-mutilation or unreported accidents; the needles are often painless once the entry wound has healed.[11]

We report a case of the late development of con-

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strictive pericarditis after self-mutilation with sewing needles. There were no acute problems at the time of needle insertion.

Case report

A 34 year old mentally retarded woman presented with a three year history of bilateral ankle oedema and a nine month history of increasing exertional dyspnoea and orthopnoea. A report from her residential institution showed that for a three year period six to nine years before she had attracted attention to herself by pushing sewing needles into her anterior chest wall. This practice had subsequently ceased and no acute problems had occurred at the time.

Her blood pressure was 100/70 mm Hg with a low volume pulse in sinus rhythm and an impalpable apex beat. Her jugular venous pulse was raised to her ears. She had with gross ankle oedema, ascites, and the liver could be felt 10 cm below the costal margin.

INVESTIGATIONS

Her haematological and biochemical profiles were normal. Chest *x* ray showed upper lobe venous distension with a cardiothoracic ratio of 150/310 and multiple sewing needles in the thorax (fig 1). Cross sectional echocardiography showed a dilated left atrium and a well functioning left ventricle with rapid diastolic outward movement and plateau. No pericardial thickening could be identified.

Cardiac catheterisation showed equalisation of diastolic pressures through all four chambers: right atrium mean 26 mm Hg; right ventricle 46/26 mm Hg; pulmonary capillary wedge pressure mean 26 mm Hg, left ventricle 110/26 mm Hg, with a rapid y descent on the right atrial pressure tracing. Angiography showed that the systolic function of the left ventricle was normal but diastolic filling appeared to be abruptly restricted. Needles were seen close to major vessels and one needle appeared to move within the aortic wall. Her coronary arteries were normal.

Ungated computed tomography showed a pericardium of normal thickness with no evidence of septal angulation. There was an area of heavy calcification in the pericardium within the atrioventricular groove at the acute margin of the heart (fig 2). The liver was enlarged with considerable fatty infiltration.

On the basis of these findings she underwent pericardiectomy. The diagnosis was confirmed when at operation the heart herniated through the incision in an extremely tight and thickened pericardium.

There were areas of adhesions at the acute margin of the heart and within these adhesions two sterile abscess cavities with heavily calcified walls were found. One cavity about 1·5 cm in diameter lay, as predicted by computed tomography, in the atrioventricular groove where the right coronary artery was clearly visible in its floor. A second cavity of similar dimensions was found between the apex and diaphragm. As expected from the aortogram a sewing needle was found embedded in the adventitia of the ascending aorta. This was removed but no attempt was made to search for or remove other needles. There were no needles within the abscess cavities.

She made an uneventful recovery with a good symptomatic response.

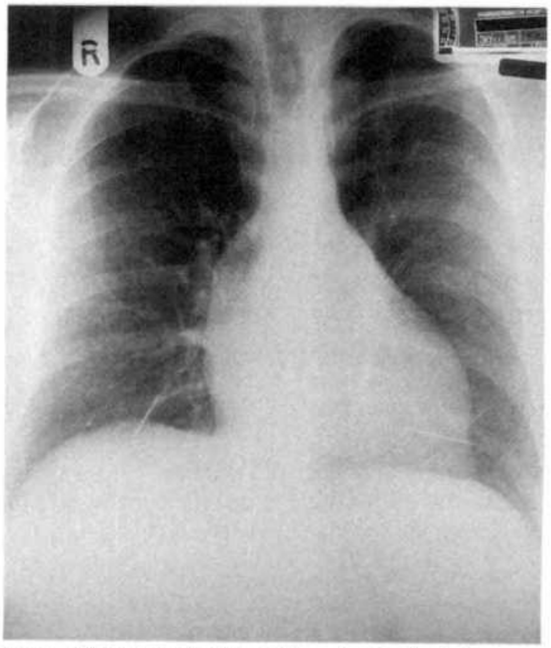

Fig 1 *Chest x ray showing many sewing needles in the thorax.*

Discussion

There are few reported cases of constrictive pericarditis after penetrating injury.[6 13 16–18] In one case constrictive pericarditis followed transpulmonary migration of a nail.[19] Paul Wood was unable to detect the development of constrictive pericarditis in a single instance in a series of thirty stab, bullet, and shrapnel wounds of the heart despite an adequate follow up.[20] Of the cases of direct pericardial needle injuries reported above only two developed constrictive pericarditis. The first resembles our case: this was another mentally ill

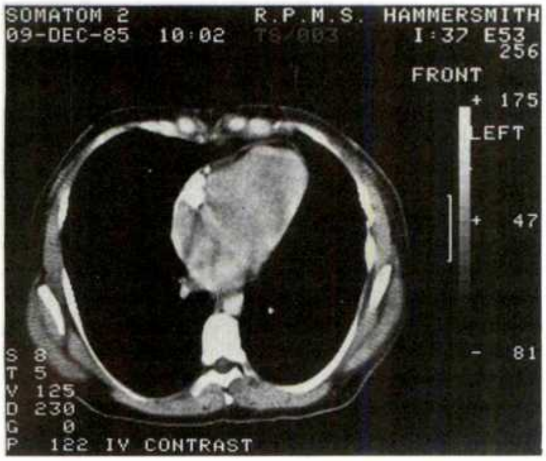

Fig 2 *Computed tomogram of the chest showing an area of heavy calcification in the atrioventricular groove. The pericardium is of normal thickness.*

patient who inserted sewing needles into her chest.[6] In this instance, however, the constriction developed five months later and was clearly a sequel to acute pericarditis resulting from the insult. In the other case constrictive pericarditis followed the loss of an intracardiac needle during a cardiac arrest and took six years to develop.[13] In the second case the only insult to the pericardium was from the needle, since cardiac massage was not required at the arrest and there was no history of acute pericarditis. In our case constrictive pericarditis took a similar time (seven years) to develop and also was not associated with any acute symptoms.

The causes of constrictive pericarditis are legion[18,21,22] and the aetiology often remains obscure even after a thorough clinical and pathological assessment. In our patient there was nothing to suggest a metabolic or infective origin. In particular, there was no evidence in the history or chest *x* ray to implicate tuberculosis. Recognition that constrictive pericarditis may result from blunt chest trauma and haemopericardium is growing.[23-26] It is also known that post-traumatic calcific pericarditis may ensue.[27] So although we cannot be certain that the constriction was a direct consequence of the needles, the balance of probability suggests a causal relation.

The cause of constrictive pericarditis when needles are present is unclear. Various authorities believe that haemopericardium alone can cause constriction.[18,28] However, the negligible incidence of constrictive pericarditis after cardiac surgery or pericardial aspiration militates against this concept.[29] Furthermore, several experimental studies in dogs have failed to support this theory. Instillation of autologous blood into the pericardial cavity of dogs did not produce constriction or adhesions although some pericardial thickening was produced when the lipid fraction of pooled dog blood was injected into the pericardial cavity.[30,31] When the haemopericardium is produced by damage to the pericardium or epicardium or both there can be evidence of constrictive pericarditis, indicating that some form of damage to the mesothelial lining is required as well as a haemopericardium for the development of constriction.[32,33] This is further supported by the observation that hot saline (105°F (39·9°C)) in the pericardial sac can induce dense adhesions, which do not occur with isothermic saline.[31] Presumably the continued presence of a foreign body within the pericardium, possibly combined with low grade chronic infection provides sufficient pericardial irritation and mesothelial damage to induce the formation of dense adhesions and chronic constriction.

The ability of needles to migrate through tissues is remarkable. Muskat reported several cases in which *x* ray examination showed how needles can rapidly traverse the tissues and he was able to reproduce migration experimentally in animals.[34] There are reports of inhaled and swallowed needles migrating into the pericardium[14] and of swallowed needles escaping from the body through the skin of the chest[35] and abdomen[36] after months or years. The combination of migration and systolic gripping action of the myocardium can rapidly suck a needle into the chest, making retrieval extremely difficult or impossible without an open heart operation.[5,37,38] In one exceptional case an attempt to remove a needle from the heart was abandoned because the needle could not be seen after pericardiotomy although the eye of the needle could be felt in the substance of the heart above the apex. Three weeks after the operation the needle appeared in the third left intercostal space and was successfully removed.[39]

The view has been expressed that all foreign bodies should be removed irrespective of symptoms, or the timing of the injury, on the basis that "late embolic, inflammatory and septic sequelae from retained pins and needles are real and transcend the risks from striving for surgical retrieval of these objects".[11] We have not found sufficient evidence of late complications to support this view. Given the state of present imaging techniques we feel that the timing of surgical intervention should be determined by the patient's clinical condition. The potential for rapid migration necessitates accurate preoperative imaging and may make location and removal of a needle from the myocardium difficult without cardiopulmonary bypass. Thus surgical intervention is best avoided unless grave manifestations are present. If the symptoms are less severe it is reasonable to adopt a conservative approach in the knowledge that with time most foreign bodies become safely encysted and do no harm.

Finally, if a patient is physically well it is important to consider their state of mind before attempting surgical retrieval, because the patient may insert more needles after operation.[11] Also the knowledge that a sharp foreign body lies near their heart may lead to the development of further psychiatric symptoms.[23 40]

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Marfan's syndrome and isolated aneurysm of the abdominal aorta

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SUMMARY A 43 year old woman presented with an aneurysm of the abdominal aorta. Marfan's syndrome was diagnosed as the underlying cause of the aneurysm. An isolated aneurysm as presenting sign of Marfan's syndrome is rare. In a review of published reports about 30 cases were found.

Marfan's syndrome is a congenital disorder of connective tissue that can affect the skeleton,[1] the eyes,[2] and the cardiovascular system.[3] The cardiovascular manifestations of this syndrome can be life threatening[4]; as a rule death is caused by aortic and mitral valve incompetence, aortic dissection, aneurysmal rupture, mural complications of an ascending aortic aneurysm, or subacute bacterial endocarditis.[4]

The aneurysm associated with Marfan's syndrome is usually localised in the ascending aorta, although it may be found at several other sites. An aneurysm of the abdominal aorta is, however, rare.[4] In this report a patient presenting with an isolated infrarenal aneurysm of the abdominal aorta is described. She was successfully operated on, but in the follow up period other severe cardiovascular complications developed that led to sudden death five months after operation.

Case report

A 43 year old woman was admitted to hospital because of a continuous pain in the abdomen. The pain had developed suddenly in the week before admission. The intensity of pain in the umbilical region had increased. She had vomited once.

The patient was remarkably tall (1·86 m) and thin. Her blood pressure was 130/70 mm Hg and the pulse rate was 100 beats per minute. The lungs were clear; there were no signs of cardiac failure. A pulsatile mass 6 cm in diameter was palpable in the midline of the abdomen. Findings suggestive of Marfan's syndrome were lumbar scoliosis and arachnodactyly.

Laboratory data were normal. An infrarenal aneurysm was demonstrated by ultrasonography and aortography (fig 1). The heart, mediastinum, and the thoracic aorta were normal on the chest *x* ray as well as the conventional ultrasound scan in so far as assessment was possible.

At laparotomy an aneurysm (8 cm long and 5 cm in diameter) was found; the calibre at the aortic

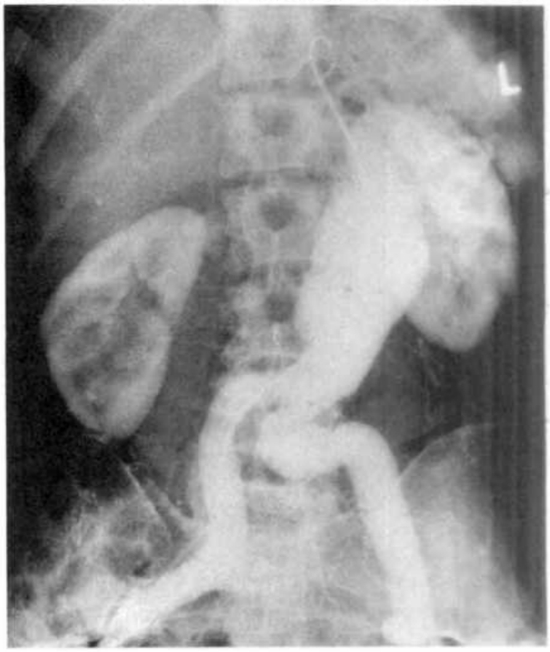

Fig 1 *Aortogram showing an infrarenal aneurysm; the calibre at the aortic bifurcation is normal.*

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bifurcation was normal, but the iliac arteries were slightly dilated. The affected segment of the aorta was replaced by a woven Dacron tubular graft.

Histological examination of the aneurysmal wall showed severe degeneration of the elastic fibres of the aortic tunica media and accumulation of mucopolysaccharides.

The postoperative course was uncomplicated; the patient was discharged 13 days after operation.

Four months later ultrasonography of the abdominal aorta and the graft showed no abnormalities. The rest of the aorta was not checked, however. Five months after the operation she was readmitted because of sudden chest pain and severe dyspnoea. Her blood pressure was 100/30 mm Hg and the pulse rate was 120 beats per minute. On the chest *x* ray the mediastinum was not enlarged. Ultrasonography of the abdominal aorta, however, showed a loose fragment in the proximal subdiaphragmatic segment, resembling the lower part of a dissecting thoracic aneurysm (fig 2). Operation was not attempted and she died soon after admission.

A postmortem examination showed a dissecting aneurysm attributable to a 4·5 cm tear in both the intima and the tunica media, starting approximately 1·5 cm above the aortic valves. The dissection extended into the left coronary artery and downwards to the level of the renal arteries and affected the left renal artery. There was severe pulmonary oedema; there were no obvious macroscopic changes in the heart and the area surrounding the aortic Dacron graft was normal. Histological examination of the aorta at the level of the dissection showed severe degeneration of the elastic fibres of the tunica media and accumulation of mucopolysaccharides.

Discussion

Marfan's syndrome is fairly readily diagnosed when the classic features are present, but formes frustes are difficult to detect and define. As a rule, all aspects of the syndrome are not expressed in one patient. This patient presented with an abdominal aortic aneurysm. She was not known to have Marfan's syndrome; the family history was negative, there were no ocular abnormalities and only a few skeletal features characteristic of Marfan's syndrome were present. According to Pyeritz and McKusick, however, two positive criteria are sufficient for the diagnosis.[5]

An aneurysm of the elastic arteries is characteristic of the vascular manifestations of Marfan's syndrome. The aneurysm is frequently located in the ascending aorta; a concomitant weakness of the aortic ring almost always leads to aortic regurgitation.[4] Aortic lesions tend to be the predominant sign in adults,[4] while mitral regurgitation is more common in children.[6]

There are twice as many elastic fibres in the ascending aorta as in the abdominal aorta. Since the ascending aorta is also subjected to pressure changes this might explain the frequent development of aneurysms in the ascending aorta.[7] Moreover, this portion of the aorta has the largest diameter and, according to the law of Laplace, is therefore exposed to the greatest wall tension.

Though aneurysms may develop at a number of

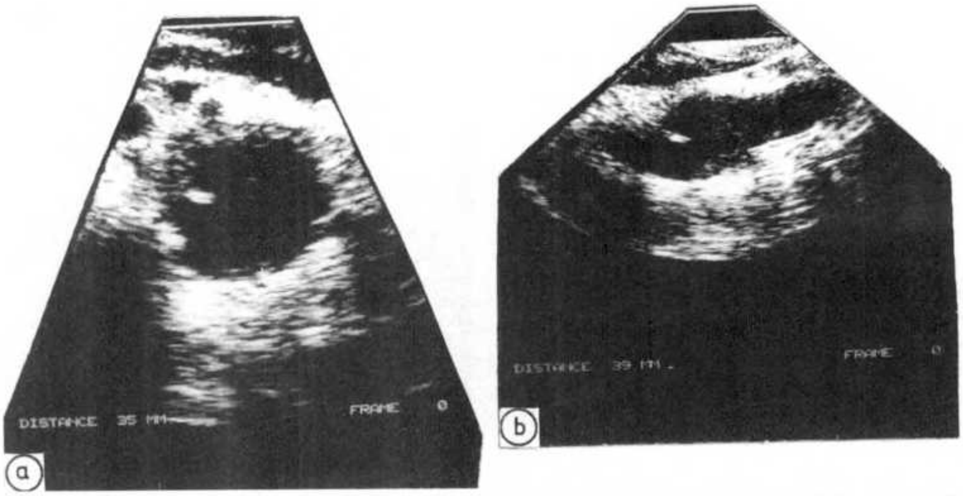

Fig 2 *Ultrasonograms showing a dissection extending into the subdiaphragmatic segment of the abdominal aorta.*

locations in elastic arteries, it is rare for a Marfan patient to present with an aneurysm of the abdominal aorta.[4] Massumi *et al* reviewed reports published before 1967.[8] They found 19 cases of abdominal aortic aneurysms in patients with Marfan's syndrome, nine of whom presented with an isolated aneurysm. Since 1967 12 patients with an abdominal aortic aneurysm have been described.[9–20] In some cases the aneurysm developed after resection of an ascending aortic aneurysm.[10–13]

Since the probability of rupture is high for patients with Marfan's syndrome,[14] immediate operation is recommended. Treatment of an abdominal aortic aneurysm before rupture is relatively simple. In the present patient a woven Dacron tubular aortic graft was used. Careful handling of the friable tissues is important. Some recommend reinforcement of the suture line with Teflon pledgets.[10]

In the present case the operation was successful and the patient had no complaints four months later. However, the follow up procedure was inadequate because it did not include echocardiography of the aortic root.[8] She died of a dissecting thoracic aneurysm five months after operation. This case underlines the fact that Marfan's syndrome is invariably progressive. The nature of the biochemical defect in the connective tissue leads to other cardiovascular abnormalities. In his series Crawford found that 50% of Marfan patients required another operation within one to ten years.[9] Because cardiovascular abnormalities are difficult to detect with routine auscultation, phonocardiography, and chest *x* rays,[8] patients must be screened, at least every four to six months, by means of cross sectional echocardiography with special attention directed toward the aortic root.[10 11 21–23] R E Pyeritz (1987, personal communication) makes a total aortic magnetic resonance scan of each new patient and scans again at regular intervals after surgical replacement of the ascending aorta.

A dilated aorta is subject to dissection.[22 24] The relative risks of dissection and rupture, as indicated by the aortic diameter, are not known precisely[25]; in fact dissection may occur in a previously normal aorta.[7] Histologically obvious tears have been found in the ascending aorta just above the aortic valves, as in our patient.

Until recently the prognosis for patients with Marfan's syndrome was poor. The hazards of surgical treatment are considerable. The encouraging results reported in the past few years justify a more vigorous surgical approach.[9 11] Therefore, thorough evaluation and follow up of patients with Marfan's syndrome are needed. Operation is the only way to improve their life expectancy.

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Br Heart J 1988;59:85–144

Proceedings of the British Cardiac Society (Golden Jubilee Meeting)

THE AUTUMN MEETING of the British Cardiac Society was held at the Wembley Conference Centre, London, on Tuesday to Thursday, 24 to 26 November 1987. The President, E SOWTON, took the Chair during private business. The scientific sessions were under the chairmanship of D N ROSS.

Abstracts of papers

Studies on ventricular fibrillation: spectral analysis and optimisation of defibrillation

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Fast Fourier transform analysis was used to study the ventricular fibrillation waveform in greyhounds and in man. The dominant frequency of canine fibrillation recorded from a surface lead remained over 9 Hz for 70 seconds, and then rapidly fell to about 5 Hz; the time courses of fibrillation induced by acute myocardial ischaemia and reperfusion were similar. Fibrillation induced by administration of ouabain or potassium was significantly slower. The time courses of fibrillation recorded from the body surface and from the epicardium of the heart were similar, but fibrillation recorded from the endocardium did not show the rapid fall in frequency after one minute. The dominant frequency of ventricular fibrillation due to acute myocardial infarction in man (6·4(0·2) Hz) was lower than in the dog (12·3(0·2) Hz). In dogs, pretreatment with lignocaine significantly reduced the dominant frequency of electrically induced ventricular fibrillation. Pretreatment with verapamil prevented the rapid fall in frequency seen after one minute in the untreated animals. Synchronisation of the defibrillation countershock to the peak or trough of the fibrillation waveform was possible, but appeared to be of no clinical value.

Antiarrhythmic drugs have significant effects during ventricular fibrillation. It is possible that calcium antagonist drugs may have a role in resuscitation from prolonged fibrillation.

Epicardial repolarisation sequence and T wave configuration

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The association of ventricular repolarisation sequence and T wave configuration in man is unclear. Epicardial activation and repolarisation sequences were studied in 19 patients, 14 undergoing coronary artery bypass grafting (upright T waves) and five undergoing aortic valve replacement (four patients T inversion). In patients with upright T waves, an inverse relation was observed between monophasic action potential duration and activation time. As a consequence, activation and repolarisation proceeded in opposite directions—mean activation sequence was from septum to free wall and from apex to base, whereas mean repolarisation sequence was from base to apex and from free wall to septum. Dispersion of repolarisation (14 ms) was less than dispersion of activation (23 ms). In patients with T wave inversion due to aortic stenosis, there was no association between action potential duration and activation time; repolarisation sequence resembled activation sequence and dispersion of repolarisation was greater than dispersion of activation (31 and 26 ms, respectively). Four patients underwent ventricular pacing to induce T wave discordance; repolarisation sequence was determined by activation sequence and dispersion of repolarisation increased.

The normal concordance of QRS and T waves of the surface ECG is due to an inverse relation between action potential duration and activation time. This relation reduces dispersion of repolarisation and may be a fundamental intrinsic antiarrhythmic mechanism.

Development of an implantable method for rate independent recognition of cardiac rhythm

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The reliance of implantable pulse generators upon heart rate analysis for diagnosing the underlying cardiac rhythm leads to errors of both inappropriate pacing and unwanted witholding of pacing. A method for diagnosing the heart's rhythm by analysing intracardiac electrogram morphology has been developed. Detecting the pattern of the slopes or gradients of which electrograms are composed after digitisation and first differentiation, it has been refined from a system which analysed recorded signals to an economical program of less than 500 bytes. This program (gradient pattern detection) reliably detects arrhythmias at atrial and ventricular level in real time and can vary the response to up to four different arrhythmias in one patient. Variations in heart rate, respiration, and posture do not significantly affect the recognition process, but electrode site may be crucial.

At selected endocardial sites, analysis of electrogram configuration by gradient pattern detection operates at sufficient speed and with sufficient reliability to supplement heart rate analysis in implantable pulse generators.

Assessment of left ventricular performance during percutaneous transluminal coronary angioplasty (PTCA) using intravenous digital subtraction ventriculography

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Left ventricular (LV) performance was studied in 52 patients during PTCA. Digital subtraction left ventriculography, after right atrial contrast injection, was performed before and during balloon coronary occlusion, and after the procedure in 37 patients. Twelve lead ECG was monitored throughout. During balloon inflation LV ejection fraction (EF) decreased in all but one patient (mean LVEF 73% to 57%, $p<0{\cdot}001$), although ST segment alteration (>1 mm) developed in only 33. The fall in LVEF correlated with the magnitude of both ST segment elevation ($r=0{\cdot}637$, $p<0{\cdot}001$) and ST depression ($r=0{\cdot}396$, $p<0{\cdot}01$). The decrease in LVEF was similar in patients with single and multivessel disease (16% and 17%, NS), and was not different during 20 and 60 second balloon occlusions (16% and 15%, NS). LV end systolic volume (ESV) increased (44 to 76 ml, $p<0{\cdot}001$) while end diastolic volume did not change (140 to 148 ml, NS). In contrast, mean R wave amplitude fell (10·1 to 8·9 mm, $p<0{\cdot}001$). There was an inverse correlation between change in LVESV and R wave amplitude ($r=-0{\cdot}371$, $p<0{\cdot}05$). In patients undergoing single LAD PTCA ($n=27$), the fall in LVEF in the 15 without collateral vessels (23%) was greater than that in the 12 patients with collaterals (12%, $p<0{\cdot}01$). There was an inverse correlation between the degree of collateral supply and both the fall in LVEF ($r=-0{\cdot}446$, $p<0{\cdot}01$), and the magnitude of ST alteration (ST elevation: $r=-0{\cdot}680$, $p<0{\cdot}001$; ST depression: $r=-0{\cdot}444$, $p<0{\cdot}025$). Both LVEF and regional wall motion returned to baseline values after the procedure.

Intravenous digital subtraction ventriculography is a sensitive method of examining LV performance during PTCA. In addition to showing the protective role of collateral vessels, it may be used to assess techniques designed to reduce myocardial ischaemia during balloon coronary occlusion.

Effect of physical training on blood pressure and baroreflex sensitivity in borderline hypertensive subjects

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The effect of physical training on blood pressure is controversial. Little is known of the effects of training on baroreflex sensitivity. Sixteen borderline hypertensive subjects were studied. Each subject was studied twice. Eight subjects were studied before and after a six month training programme, and the other eight after training, and then after a four month detraining period (loss of fitness). Measurements were taken of baroreflex sensitivity and intra-arterial blood pressure at rest, during mental arithmetic, during isometric exercise, and during dynamic exercise. Thirteen subjects also underwent ambulatory blood pressure measurement. For all 16 subjects increased fitness was associated with a fall in resting blood pressure from 148(1·0)/82(0·7) mm Hg to 138(0·8)/76(0·8) mm Hg ($p<0{\cdot}001$). Baroreflex sensitivity rose from 14·0(1·8) to 17·5(2·0) mg/mm Hg ($p<0{\cdot}05$) with increased fitness. Fitness did not, however, attenuate the blood pressure response to mental stress, resulting in a greater absolute blood pressure increase. Fitness did result in lower diastolic pressures during isometric and dynamic exercise. With increased fitness ambulatory blood pressure fell from 141(3·0)/89(1·6) mm Hg to 136(3·3)/81(2·9) mm Hg ($p<0{\cdot}01$). These changes in blood pressure could not be explained by changes in weight or sodium or potassium intake.

We conclude that physical conditioning is an effective approach in the management of borderline hypertension.

Intracellular calcium release initiates spontaneous calcium transients in vascular smooth muscle

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Fluorescence measurements of calcium indicator signals (Fura 2 and Quin 2) from aortic smooth muscle cells in primary culture have shown spontaneous transient increases in intracellular calcium concentration. The transients consist of a rapid increase in intracellular calcium concentration of approximately 100 nmol/l which is sustained for approximately 30 seconds. The frequency of the transients can be modulated by low concentrations of vasoactive substances. Experiments are described which show that the transients are due to a spontaneous release of calcium from the sarcoplasmic reticulum followed by an influx of calcium through voltage dependent channels. No spontaneous influx occurs in the absence of an initial intracellular release of calcium. These findings are the first to show that: (a) the sarcoplasmic reticulum can spontaneously release calcium into the cytoplasm in the absence of receptor stimulation, and (b) that this release can initiate activation of voltage dependent channels. The findings support the view that the sarcoplasmic reticulum is the major system controlling cytoplasmic calcium in vascular smooth muscle cells and they provide a biochemical explanation for the spontaneous contractions frequently observed in intact vessels, including human coronary arteries.

This mechanism probably has a fundamental role in the regulation of vascular resistance and the development of coronary spasm.

Intravenous and intrapulmonary recombinant tissue type plasminogen activator (rt-PA) in treatment of acute, massive, pulmonary embolism: a multicentre pilot study

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Eight centres participated in a pilot study which compared intrapulmonary (PA) with intravenous (IV) treatment by recombinant tissue type plasminogen activator (rt-PA) in 34 patients with angiographically proved acute (<5 days), massive, pulmonary embolism. All patients received intravenous heparin in a bolus of 5000 IU followed by 1000 IU/h. After 50 mg rt-PA given over two hours the severity of embolism, determined from pulmonary angiograms, declined by 12% in the PA group and 15% in the IV group. After a further 50 mg given over five hours (22 patients), the angiographically determined severity had decreased by 38% from baseline in the PA group and by 38% in the IV group. Measured haemodynamic variables showed major improvement with normalisation of pulmonary artery pressure after a seven hour treatment with 100 mg rt-PA. Fibrinogen concentrations dropped 46% from baseline after 50 mg and 66% from baseline after 100 mg rt-PA. Minor bleeding, most often limited to puncture sites, was noted in 12 patients. Four other patients, however, required a transfusion of two or more units of blood; all of them had been operated on an average of seven days (range 2–13) before thrombolytic treatment was started. In seven other patients thrombolytic treatment was started a mean of 8·5 days (range 3–15) after operation and no bleeding was seen.

In a dose of 100 mg rt-PA results in appreciable lysis of pulmonary emboli. This effect is seen within eight hours of the start of treatment and intravenous administration was as effective as intrapulmonary. rt-PA is only relatively fibrin selective but there was major bleeding in only 12% of patients.

The benefit of very early intravenous streptokinase administration in acute myocardial infarction

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Fifty one patients (age range 38–73; mean 54·2 years) who had received early intravenous streptokinase were divided into two groups: those whose pain before streptokinase lasted less than 90 minutes (group A: 23 patients) and those whose pain lasted 90 minutes to 4 hours (group B: 28 patients). Exercise thallium scintigrams were performed following discharge and scored visually in nine regions (0 = no defect, 3 = severe defect). In group A the myocardial defect score was lower (mean: group A 4·7(0·6); group B 6·6(0·7); $p < 0\cdot05$) as was the infarct related zone score (group A 1·3(0·2); group B 2·1(0·3); $p < 0\cdot05$). Thirty two of the patients were also assessed by a quantitative circumferential profile technique. The severity index was the area between the patients profile and normal. The total myocardial severity index (group A 559(81); group B 992(164); $p < 0\cdot03$) and the infarct related severity index (group A

797(496); group B 1616(277), $p<0.01$) were also significantly lower in group A.

Exercise thallium scintigraphy showed that there was an improvement in patients who received early streptokinase for myocardial infarction and emphasised the need for the administration of this agent as soon as possible after the onset of pain.

Reperfusion arrhythmias are uncommon during thrombolysis in acute evolving myocardial infarction

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Arrhythmias are commonly associated with reperfusion in animal studies but the clinical relevance remains uncertain. We performed continuous frequency modulated electrocardiographic recordings immediately after admission to Casualty in 38 of 45 consecutive patients presenting within four (mean 2·5) hours of the onset of acute myocardial infarction and who had emergency coronary arteriography and intracoronary thrombolysis with streptokinase. All patients received diamorphine and high doses of nitrates but no prophylactic antiarrhythmic drugs. In 19 patients 36 episodes of intermittent reperfusion were observed and stable reperfusion was achieved in 32 patients. Arrhythmias occurring within five minutes before or after ST segment resolution and coronary recanalisation on arteriography were defined as reperfusion arrhythmias. Transient reperfusion arrhythmias were seen in six patients during 11 of the 68 episodes of reperfusion with ventricular fibrillation (VF) in two patients, ventricular tachycardia (VT) in two, idioventricular rhythm (IVR) in two, frequent ventricular ectopics (VEs) in three, and bradycardia in two. During persistent ST segment elevation before reperfusion in 32 patients, arrhythmias were observed in 21 with VF in three (in two during cardiac catheterisation), VT in 14 (8), IVR in 4 (2), VEs in 11 (7), AF in 5 (3) and bradycardia in 2(2). During the two hours after stable reperfusion, arrhythmias occurred in 12 patients, with VF in two, VT in seven, IVR in five, VEs in seven, AF in two and bradycardia in one.

Arrhythmias are commonly observed in patients during evolving acute myocardial infarction and thrombolysis, but specific reperfusion arrhythmias are not common.

Pre-hospital thrombolytic treatment with streptokinase for acute myocardial infarction in England, a cost effective treatment: comparison with secondary prevention using β blockade

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Intravenous streptokinase achieves both reperfusion and improvement of prognosis in acute myocardial infarction. The purpose of this study was first to estimate the effect and cost if this policy were applied nationally and treatment was started before hospital admission. Secondly, this study compared the efficacy of this treatment with one year's secondary prevention treating survivors with β blockers. In England during 1985 there were 99 400 deaths attributed to acute myocardial infarction. Deaths in hospital were 26 800; 72 600 died outside. Hospital admissions were 107 000. Thus total infarcts were at least 179 600. A previous study has shown that β blockade started about the time of hospital discharge could at best provide a potential saving of 2480 lives in one year if all 80 000 survivors could be treated. The cost would be about £5 028 000, an average of £2030 per life saved. The cost of treatment with streptokinase (1·5 million units) is approximately £100 per patient. If all infarcts were treated with streptokinase outside hospital and there was a 20% reduction in mortality there would be a saving of 19 900 lives at a cost of £17 960 000, £900 per life saved. This is eight times the best improvement in lives saved that could be expected with one year's treatment with β blockade. More realistically, if 30% of the annual number of infarcts (53 900) were treated with streptokinase before hospital admission 5960 lives could be saved at a cost of £5 390 000.

For about the same cost, pre-hospital streptokinase treatment could save 2·5 times the number of lives as one year's secondary prevention with β blockers.

Thrombolytic treatment in acute myocardial infarction: acute ischaemic events during long term follow up

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Although thrombolytic treatment is widely used in myocardial infarction, late coronary reocclusion may expose the patient to the risk of further ischaemic events. We have examined the incidence of acute ischaemic events in 44 patients with angiographically proved coronary recanalisation after myocardial infarction. Twenty six patients (group A) received early revascularisation (percutaneous transluminal coronary angioplasty n = 20, coronary artery bypass graft (n = 6) at 17(5) days and 18 (group B) were treated conservatively. The treatment allocation was arbitrary and determined principally by the referring physicians. Nevertheless there were no significant differences between groups A and B in infarction location, number of diseased vessels—1·9(0·2) and 1·6(0·1), respectively—or duration of follow up—16(2) and 13(3) months, respectively. There was a total of nine acute ischaemic events (death 2, myocardial infarction 4, unstable angina 3) affecting 20% of the patients during a follow up period of 15(2) months. Of the nine events, however, eight occurred in group B compared with only one (unstable angina) in group A ($p < 0·01$).

The infarct patients included in this study all had proved coronary recanalisation and were therefore a potentially high risk group for further ischaemic events. The data, however, indicate that the incidence of events was not excessive in relation to the expected incidence in other survivors of myocardial infarction. Indeed, in patients treated with early revascularisation the incidence of acute ischaemic events during follow up was strikingly low.

Early versus late recombinant tissue plasminogen activator (rt-PA) in acute myocardial infarction

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Twenty nine consecutive patients (5 women, 24 men) mean age 58 years (range 37–74) with myocardial infarctions (MI) of < 4 hours duration were randomised when first seen to receive either 100 mg rt–PA over 90 minutes followed by 50 mg over 3½ hours (group A, n = 14) or to placebo (group B n = 15). On admission, patients who had received placebo were given rt–PA and vice versa via an infusion running concurrently with the first infusion. On average rt–PA started 110 minutes after the MI in group A and 192 minutes in group B. Cardiac catheterisation was performed at a mean of 10 days for group A patients and 11 days for group B. MI related vessel patency was assessable in 13 patients from each group. Of 13 in group A, 10 had TIMI grade 2 or 3 compared with 6 of 13 in group B. Mean global ejection fraction (GEF) for group A was 49% and 44·5% for group B. For those with anterior MI (group A) mean GEF was 44%; it was 45% for those in group B. For those with inferior MI (group A) mean GEF was 52% compared with 48% for those in group B. Regional wall movement in right anterior oblique 30° view was assessed by the Leighton method. Patients in group A had a mean of 3·5 hypokinetic segments compared with 3·9 for group B. Mean percentage shortening of segments 2 and 3 in patients with anterior MI was 18% for group A and 14% for group B. Mean percentage shortening of segments 7 and 8 in patients from group A with inferior MI was 13% compared with 6·5% in patients from group B. There were no important bleeding complications. Five patients had reocclusions—one in group A and four in group B. During their stay in hospital two patients (one from each group) died from cardiac disease.

Rt–PA is an effective thrombolytic agent that can safely be given outside hospital. Early administration suggests better reperfusion rates and improved left ventricular function but a larger number of patients are required to verify these results.

Post infarction ventricular septal defect: value of colour flow mapping

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Previous ultrasound studies of post infarction ventricular septal defects (PIVSD), restricted to duplex scanning have suggested important limitations inherent in the technique. Potentially colour flow mapping (CFM) should solve these problems by accurately confirming both defect site(s) and VSD jet direction, thus allowing more accurate non-invasive haemodynamic assessment. We report a prospective correlative study comparing both techniques in which 30 patients with PIVSD (22 new, eight recurrent) were studied both before and after operation. Duplex information was available in all 30 and CFM in 13. The defect was imaged by cross sectional echocardiography in only five studies (one inferior, three apical, one central PIVSD). Duplex scanning correctly showed a right ventricular flow disturbance diagnostic of PIVSD in 29 studies, but failed to locate the defect in 12 cases and provided ambiguous haemodynamic data in 19. In contrast CFM consistently predicted defect site as well as jet width, direction, and number of discrete defects. Three differing CFM patterns diagnostic of (a) inferior, (b) apical, and (c) central PIVSD were defined. Evaluation of PIVSD flow velocity profiles showed a number of differing shunting patterns—pandiastolic shunting was a consistent feature with variable late diastolic shunt reversal. PIVSD jet velocity (n = 29) was found to be less accurate in right ventricular pressure estimation than tricuspid incompetence velocity. Both early (n = 2) and late (n = 5) patch dehiscence and the development of further septal rupture (n = 2) were accurately predicted.

We conclude that colour flow mapping has significant advantages over non-CFM duplex scanning and is the ideal non-invasive technique for the identification and assessment of PIVSD both before and after operation.

Colour flow Doppler ultrasound in assessment of prosthetic valve function: an interim analysis

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We have used colour flow Doppler ultrasound (CFD) to study 90 prostheses in 80 patients over a six month period. We used a Hewlett Packard system with threshold enhanced and variance maps, a 1·9 MHz continuous wave (CW) and 2·5 MHz duplex transducers. The study was conducted as follows: cross sectional echocardiography, CFD, pulsed Doppler, and CW. Normal function was defined clinically and by normal pressure half times and transvalve velocities, or both. Regurgitation was shown by a jet with multiple aliasing. It was considered paraprosthetic (P/P) if a thread of colour was seen outside the sewing ring and through the valve if the jet was seen within the orifice on at least two views. All normal mitral prostheses had mosaic aliasing and variance throughout diastole. Characteristic inflow patterns for Bjork-Shiley (n = 9), Carpentier-Edwards (n = 13), and Starr-Edwards (n = 7) prostheses were shown. Mitral regurgitation was not detected. In normal aortic prostheses Björk-Shiley valves (n = 14) had minor regurgitation through the valve in 12, and Carpentier-Edwards valves (n = 11) had mosaic aliasing through the whole orifice and no regurgitation. In abnormal valves clinically unsuspected regurgitation was found in six mitral and 11 aortic valves. Thirteen had small P/P leaks and four had leaks through the valve. Three further valves had regurgitation on CW but not on CFD. Catheterisation in five cases validated the site of regurgitation by CFD. Ten patients with regurgitation previously detected but not localised by conventional Doppler were reexamined by CFD with successful localisation in nine.

Our initial experience shows CFD to be useful for quick detection of small unsuspected leaks, localisation of leaks, and visualisation of flow direction. Very small leaks may not be detected.

Extent of myocardial uptake of indium-111 monoclonal antimyosin antibody and ECG location of acute myocardial infarction

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The diagnostic role of indium-111 labelled monoclonal antimyosin antibody (^{111}In-AM) antigen binding fragment (Centocor) was assessed in 50 consecutive patients with suspected acute myocardial infarction (AMI). Serial creatine kinase enzyme release, 12 lead ECG, and ^{111}In-AM uptake were measured in all patients. ^{111}In-AM (2mCi) was injected intravenously within 48 hours of the onset of chest pain. Imaging was performed in multiple views at 24 and 48 hours after injection using a calibrated gamma camera. Strict quality control was maintained for labelling and imaging. The scans were read blind by two observers. Images were obtained in 46 patients (35 men); 32 had AMI diagnosed by at least two of three conventional criteria: chest pain, a rise in creatine kinase activity and ECG changes; 24 had transmural and eight non-transmural AMI; three had unstable angina (no AMI), and 11 had no evidence of AMI or ischaemia. All patients with AMI had positive myocardial uptake of ^{111}In-AM. One patient with non-ischaemic pain had a diffuse uptake of ^{111}In-AM, the rest of the non-AMI group had negative scans (13 of 14). Total agreement of location of infarct between ECG and ^{111}In-AM was found in 9 of 32; ECG overestimation in four of 32 (only inferior); ECG underestimation in 16 of 32; and positive scan with negative ECG in three.

^{111}In-AM is highly sensitive for detecting myocardial necrosis as determined by a rise in creatine kinase activity. The 12 lead ECG underestimates infarct size and location. ^{111}In-AM produces easily interpretable images and may be valuable for determining prognosis and infarct size.

Are multiple ventricular septal defects consistently predicted by colour flow mapping?

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Duplex scanning can accurately define both the type of ventricular septal defect (VSD) and associated haemodynamics in isolated VSDs; this may allow surgical referral on non-invasive grounds alone. One caveat to this approach has been the possibility of missing multiple VSDs. Colour flow mapping (CFM) has the potential to show the number and site of the VSDs, thus precluding preoperative angiography. To determine the accuracy of CFM diagnosis of VSDs, we have studied 31 patients with a broad range of such defects comparing CFM information with both angiographic and operative findings. Patients were analysed in two groups—group 1: 13 patients with equal ventricular peak systolic pressures and group 2: 18 patients with dissimilar ventricular pressure. In group 1 both imaging and CFM were unreliable in predicting the presence of multiple VSDs showing two or more discrete VSD jets in only eight of 13 patients. The combination of apical trabecular and single perimembranous defect was consistently predicted (all three patients) but multiple adjacent defects sited in perimembranous, muscular outlet, or muscular inlet septae were not accurately defined by either CFM or correlative left ventricular (LV) angiography. Where ventricular pressures were dissimilar (group 2) multiple defects were more accurately predicted (16 of 18 patients) but similar problem areas still existed. CFM was demonstrably better than LV angiography in this group. Multiple trabecular VSDs (not visualised by Duplex) were consistently predicted by CFM in both groups.

We conclude that CFM is a useful adjunct in the diagnosis of multiple VSDs, and, in our experience, is more accurate than LV angiography. It fails to be consistently accurate, however, in defined subsets of the multiple VSD population.

Incidence and coincidence of prosthetic valve regurgitation assessed with colour flow imaging

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Colour Doppler echocardiography has been used to assess the degree of regurgitant lesions in patients with prosthetic valves. We have observed several patients with clinically normal prosthetic valve function but with appreciable regurgitation on colour flow imaging. To assess the frequency of this finding we studied 176 patients with normally functioning aortic and mitral prostheses. In the aortic position, 38 patients had Starr-Edwards valves, 19 Bjork-Shiley, and 25 had bioprostheses In the mitral position, 50 patients had Starr-Edwards valves, 22 Bjork-Shiley, and 22 had bioprostheses. No patient was clinically in heart failure. Colour flow imaging showed the presence of aortic incompetence in 38 of 82 (67%) patients of whom 19 of 38 (50%) had Starr-Edwards, 12 of 19 (63%) Björk-Shiley and seven of 25 (28%) had bioprostheses. Mitral incompetence was detected in 15 of 94 (16%) patients of whom nine of 50 (18%) had Starr-Edwards prostheses, one of 22 (4%) Björk-Shiley, and five of 22 (23%) had bioprostheses. In only 10 patients was there clinical evidence of an aortic $(n = 9)$ or mitral $(n = 2)$ regurgitant murmur, on the basis of a well functioning prosthesis.

We conclude that mild prosthetic valvar regurgitation is found in one of three patients with normal prosthetic valves. Patients with aortic prostheses show a higher frequency of regurgitation than those with mitral prostheses $(p < 0 05)$.

Cine magnetic resonance imaging of valvar heart disease

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Regurgitant fraction can be calculated in patients with valvar disease from magnetic resonance stroke volume measurements, provided only a single valve is affected. A cine field echo sequence is more flexible as turbulent flow leads to loss of signal and to a qualitative assessment of abnormal flow patterns. We have studied 20 normal subjects and 30 patients with stenosis or regurgitation, or both, of the aortic, mitral, and tricuspid valves. Turbulence was graded proximal and distal to the valves according to its area. Regurgitant jets were not seen in the normal subjects, but there was some systolic turbulence in the aorta and diastolic turbulence in the left ventricle during rapid mitral filling. In the patients with regurgitation of a single valve, there was a good correlation between the regurgitant fraction and the grade of turbulence $(r = 0{\cdot}85)$, and there were significant differences of mean regurgitant fractions in each grade $(p < 0 01)$. The grade of turbulence agreed with the angiographic grade of regurgitation in 16 patients, but in seven it differed by one grade. Correlation was poor between the grade of turbulence in the ascending aorta and left ventricle and the pressure gradient across the aortic and mitral valves because turbulence occurred distal to abnormal but not to stenosed valves. The cine acquisition also showed details of valve disease: thickening and restricted motion of stenosed valves was apparent, and left atrial thrombus was more clearly seen than in the spin echo images.

A cine field echo sequence with spin echo volume measurements provides a good assessment of regurgitant aortic, mitral, and tricuspid valves, but turbulence distal to abnormal valves occurs irrespective of the degree of stenosis.

Risk of electromagnetic interference with pacemaker function in the aircraft environment

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The electromagnetic environment on board aircraft presents a potential hazard to pacemaker users, but the level of risk has not been defined. Electromagnetic field strengths were measured on 10 aircraft during radio and radar operation. All had very high frequency (VHF) radio, four also had high frequency (HF) radio and nine had radar. Ten different unipolar pacemakers were exposed to similar fields at strengths up to 30 V/m in a shielded chamber and the minimum field strengths for interference (abnormal pacing or reversion to interference mode) and failure (cessation of pacing for 30 seconds) were determined. The effect of modulation at 1 kHz with pulsing at 2 Hz was also examined in HF fields. In the aircraft, maximum field strengths ranged from 0·2–35·0, mean (SD) 6·55 (10·95), V/m for VHF; 0·2–1·12, mean 0·54 (0·38), V/m for HF; and 1·12–18·0, mean 7·23 (5·86), V/m for microwave. In the shielded chamber, all pacemakers were susceptible to interference and failed at some stage, often abruptly without prior reversion to interference mode. Minimum field strengths for interference ranged from 3–13, mean 5·7 (2·83), V/m for VHF; 1·5–7·5, mean 4·27 (2·24), V/m for HF; and 0·25–0·9, mean 0·5 (0·18), V/m for pulsed, modulated HF. Minimum field strengths for failure ranged from 3–22·5, mean 11·2 (6·2), V/m for VHF; 6–10, mean 7·7 (1·33), V/m for continuous wave HF; and 0·55–2·9, mean 1·51 (0·87), V/m for pulsed, modulated HF. In microwave fields, interference occurred in only one unit (at 16 V/m) and there were no failures.

It is concluded that pacemakers are susceptible to interference in electromagnetic fields comparable to those found on aircraft. The extent to which implantation offers shielding and reduces the risk to patients requires evaluation.

Refinement of risk stratification after myocardial infarction by programmed electrical stimulation of the right ventricle

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A sub-maximal exercise test (SMET) following myocardial infarction (MI) selects a group at risk of death in the subsequent year. To evaluate the role of repetitive ventricular responses (RVRs) to programmed electrical stimulation (PES) of the right ventricle in refining risk stratification, we studied 262 consecutive stable survivors of MI, all of whom undertook an early SMET: those with a positive test underwent cardiac catheterisation and PES. RVRs were sought with one or two ventricular extra stimuli in sinus rhythm or paced at 600 and 500 ms cycle lengths. Patients with a positive SMET were 13 times more likely to die in the first year than those with a negative test. In those patients with a positive SMET there were no responses to PES in 15%, up to four in 65%, between five and 22 in 14%, and 5% developed sustained ventricular tachycardia (VT) ≥10 s. No deaths occurred with the investigation. Sustained VT was independent of site and type of infarct, extent of coronary disease and left ventricular dysfunction, Lown grading of ambulatory ECGs, as well as clinical and SMET induced arrhythmias. Multivariate analysis showed that induced sustained VT was the most powerful predictor of death in the first year; patients with this response were 10 times more likely to die than those with no response.

Programmed electrical stimulation of the right ventricle for patients with a positive SMET thus strongly refines risk stratification.

First derivative of right ventricular pressure as a sensor for an implantable rate responsive VVI pacemaker

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After a preliminary series of pressure sensing non-rate responsive pacemakers, four patients mean age

69 (range 43–87) with complete atrioventricular (AV) block have now had units implanted that offer them a rate response based on changes in the first derivative of right ventricular pressure. The system (Medtronic US) consists of a special unipolar lead with pressure transducer set 3·5 cm back from the stimulation electrode. The pacemaker has two connection ports and is equivalent in size and weight to the DDD unit. Implantation technique was straightforward and in three patients qualitative pressure and first derivative of pressure wave forms were comparable between those telemetered by the pacemaker and a fluid filled manometer. Follow up (mean two months) has assessed rate responsive behaviour by exercise stress testing, Holter monitoring, and tilting. Two patients have shown occasional periods of over sensing of T waves, otherwise no complications have been encountered. Resting heart rate before exercise was a mean of 66 paces per minute (ppm) with rapid acceleration in the first minute of exercise and the mean maximum heart rate achieved was 114 ppm. The mean rate variability was 48 between rest and peak exercise, rate fall on recovery was physiological over five minutes. Mean heart rate change on Holter monitoring was from 53 to 90 ppm. Mean heart rate on tilt increased from 64 to 71 ppm at 60° head up.

In conclusion, sensing of the first derivative of right ventricular pressure for rate responsive ventricular pacing proves in practice to be physiological.

Is the optimal atrioventricular delay the same at rest and during exercise? An assessment in patients with dual chamber pacemakers

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Cardiac output is a product of heart rate and stroke volume. In a patient with a dual chamber pacemaker the pacing rate is dependent on the atrial rate, and the stroke volume depends in part on appropriate timing of atrial systole. We investigated the optimal atrioventricular (AV) interval during exercise using continuous wave Doppler. Cardiac output was calculated as the product of Doppler measured stroke distance at the left ventricular outflow (using Quinton Exerdop equipment), aortic root area (M mode echocardiogram), and pacing rate. Nine patients (average age 53, range 22–71 years) with persistent complete heart block, normal left ventricular function, and implanted dual chamber pacemakers, were studied. Pacemakers were programmed to a basic pacing rate of 70 bpm. At rest cardiac output was measured with AV intervals of 75, 100, 150, and 200 ms. Cardiac output was then measured at the peak of four submaximal exercise tests (stage I Bruce protocol), at each of the above AV intervals. At rest, cardiac output was maximum with an AV delay of 150 ms mean (SD) (5·81 (1·5) l/min), and it was significantly lower at AV intervals of 75 (5·2 (1·3) l/min, $p < 0\cdot01$) and 200 ms (5·51 (1·5) l/min, $p < 0\cdot01$). On exercise, maximum cardiac output was seen with an AV delay of 75 ms (8·26 l/min) which was significantly higher than that at AV intervals of 150 (7·46 (0·9) l/min, $p < 0\cdot05$) and 200 ms (7·85 (1·1) l/min, $p < 0\cdot05$). The changes in heart rate on exercise at all AV intervals were similar.

We conclude that the optimal atrioventricular delay is shorter during exercise than at rest. Rate modulation of the AV interval will improve the haemodynamic response in patients fitted with dual chamber pacemakers.

Atrial natriuretic peptide in different modes of cardiac pacing

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Plasma atrial natriuretic peptide concentrations are raised in congestive cardiac and renal failure, and in paroxysms of supraventricular tachycardia. We investigated 32 patients, 20 men, mean age 69 years (range 38–86) with complete heart block but no heart or renal failure. Six patients with complete atrioventricular block had atrial natriuretic peptide concentrations (mean (SEM) pmol/l) of 141 (28) unpaced, 139 (30) with ventricular pacing (VVI) for 30 days and 53 (7) with atrioventricular pacing (DDD) for 30 days. Thirteen patients paced long term VVI (mean 43 months) had atrial natriuretic peptide concentrations of 112 (13). Thirteen patients paced long term DDD (mean 40 months) had peptide concentrations of 43 (7). Thirteen age and sex matched controls had atrial natriuretic peptide concentrations of 58 (7). There was a significant difference between atrial natriuretic peptide in unpaced, VVI paced for 30 days, and long term VVI paced complete heart block at the 5% level compared with controls. There was no significant difference between atrial natriuretic peptide after both 30 days or long term DDD pacing with controls. Four patients had similar resting concentrations of atrial natriuretic peptide when paced VVI or ventricular rate responsive pacing (VVIR): 133 (34) and 134 (39), respectively. During exercise atrial natriuretic peptide concentrations were lower in

VVIR mode than VVI, 265 (110) and 334 (115), respectively, at identical exercise levels that were equivalent to peak exercise in VVI.

These results corroborate the physiological nature of DDD pacing compared with VVI and suggest that VVIR pacing offers benefit on exercise over VVI.

Comparative assessment of rate responsive pacemakers

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The majority of studies designed to assess the performance of rate responsive pacemakers (RRPs) have been based on bicycle or treadmill exercise testing. This disregards the fact that few patients voluntarily undertake sustained exercise under progressively increasing workloads during their normal daily life. We have therefore used ECG telemetry to monitor changes in heart rate during walking, climbing stairs, and a range of standardised domestic tasks in 20 patients with RRPs (mean age 58 years). These pacemakers sensed activity ($n = 12$), respiration ($n = 5$), or QT interval ($n = 3$). Pacemaker responses were compared with the normal pattern of changes in heart rate recorded from 20 healthy volunteers (mean age 61 years) undergoing the same activities. All RRPs could be programmed to produce a close approximation to the normal heart rate response during walking, but there were considerable variations in their ability to meet the requirements of short periods of exertion. For example, mean values for the peak increase in heart rate (R) during rapid stair climbing and the time taken (T) to reach this peak were as follows: *controls*—R = 58 bpm, T = 43 seconds; *activity sensing*—R = 39 bpm, T = 47 seconds; *respiratory sensing*—R = 13 bpm, T = 80 seconds; *QT sensing*—R = 31 bpm, T = 145 seconds.

The delayed responses found with respiratory and QT sensing pacemakers led to peak increases in pacing rate occurring at up to 90 seconds after the cessation of some forms of exercise. Such response patterns may give rise to symptomatic post-exertional tachycardia.

Coronary artery stenting after balloon angioplasty

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Restenosis, occurring in about one third of cases after coronary balloon angioplasty, is the major long term limitation of the technique. In an attempt to overcome this, a new flexible, self expanding stainless steel endoprosthesis has been developed and initial results have been encouraging. The stent can be inserted percutaneously using a standard angioplasty guide catheter. Immediately after successful balloon angioplasty, we have implanted four such devices in the left anterior descending coronary artery (LAD) of four male patients with either recurrent stenosis ($n = 3$) or new disease. All had good left ventricular function without previous Q wave infarction in the LAD territory. None had unstable angina, but all had exertional symptoms and a positive stress test. A good immediate angiographic result was obtained in all cases with no appreciable residual stenosis.

No early complications occurred as a result of stent implant and no fixed or transient postoperative ECG changes occurred. There have been no complications during the follow up period of one to four months. Meticulous anticoagulation was maintained continuously during and after implantation together with administration of aspirin and calcium channel blockers. In addition to describing our own experience, an overview of the data obtained by the Coronary Artery Stent Implantation Study group will be presented.

Angioplasty for occluded and disconnected coronary arteries

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Indications for percutaneous transluminal coronary angioplasty (PTCA) are expanding and have come to include totally occluded vessels. We have undertaken single vessel PTCA in 29 patients with total coronary occlusion (group 1). A further 55 procedures were performed in patients with coronary disconnection (group 2), with no visible connection between proximal and distal arterial segments despite delayed antegrade filling. In both groups 75% of patients had only single vessel disease, and 45% had had infarction in the territory of the PTCA vessel. Despite this all patients complained of troublesome angina, which was severe (grade III or IV) in 79% of group 1 and 87% of group 2. PTCA was angiographically successful in 55% of group 1 and 80% of group 2 ($p < 0{\cdot}05$); success was not influenced by the estimated duration of arterial occlusion. There were no deaths in hospital in either group. Indeed, group 1 had no major complications, but three patients in group 2 required emergency operations, and two had myocardial infarctions in hospital. Successful PTCA led to a sustained symptomatic improvement in most patients with follow up ranging up to four years.

These data indicate that patients with angina associated with coronary occlusion or disconnection respond well to PTCA. An anterograde connection between proximal and distal arterial segments significantly improves the PTCA success rate. Although total occlusion has a lower success rate the procedure is safe and symptoms will often improve if the vessel is reopened.

Effect of intracoronary nitrate and nifedipine on regional myocardial blood flow and metabolism during coronary angioplasty

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Intracoronary drugs are often given during coronary angioplasty (PTCA) as prophylaxis against coronary spasm. To investigate any cardioprotective effect we measured great cardiac vein flow (GCVF) by thermodilution, regional myocardial oxygen consumption (MVO_2), lactate extraction ratio (LER) and intra-coronary ECG changes, during four consecutive balloon inflations each of 60 seconds in 12 men undergoing dilatation of the left anterior descending coronary artery. Inflation 2 was used for control readings. Inflations 3 and 4 were undertaken 60 seconds after intra-coronary injection of 200 μg of nifedipine and 200 μg glyceryl trinitrate, respectively. Baseline readings were taken before and between inflations. During control inflation mean GCVF (ml/min) fell significantly (102 (32)–82 (30), $p < 0\cdot02$); MVO_2 (ml/min) was reduced (12·3 (4·2)–10·1 (2·5), $p < 0\cdot05$) and there was net lactate production (64 (70)–12 (92), $p < 0\cdot05$). After intracoronary nifedipine, during inflation 3 there was an increase in GCVF (94 (22)–125 (52), $p < 0\cdot02$), no significant fall in MVO_2 (11·3 (2·9)–10·9 (3·4)) and no net lactate production (29 (58)–41 (38)). There was no change over control values in GCVF (98 (34)–74 (41), $p < 0\cdot02$) or MVO_2 (11·8 (4·3)–9·5 (2·9), $p < 0\cdot05$) after intracoronary glyceryl trinitrate but the fall in LER was less pronounced (13 (75)–7 (80), NS). Continuous monitoring of the intracoronary ECG showed a reduction of ST segment rise during balloon inflation preceded by nifedipine and by glyceryl trinitrate (4·5 (2) mm and 5·5 (3) mm compared with control of 7·0 mm, $p < 0\cdot005$ and $p < 0\cdot05$, respectively).

In conclusion, balloon coronary occlusion for 60 seconds resulted in significant falls in regional myocardial blood flow, oxygen consumption, and lactate production. These changes were completely abolished by prior administration of intracoronary nifedipine. Intracoronary nitrates in this context do not affect coronary flow but may attenuate regional ischaemia to a lesser extent than nifedipine.

Use of pulsed Nd–YAG laser energy for laser assisted balloon angioplasty in man

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The risk of vessel perforation in laser assisted balloon angioplasty (with conventional continuous wave lasers) is reduced by the use of modified fibre tips, allowing lesions to be crossed which cannot be crossed by conventional means alone. Higher peak power pulsed laser energy causes less subjacent tissue damage than does continuous wave laser energy and may further reduce the risk of perforation. To assess the clinical safety and efficacy of 100 μs pulsed Nd-YAG laser energy (0·5 J pulses at 10 Hz, and peak power density of 10 MW/cm^2) delivered via a 600 μm core diameter fibre with a 2 mm diameter bullet-shaped sapphire tip, percutaneous laser assisted balloon angioplasty was performed on superficial femoral artery occlusions which could not be crossed with a guidewire, in 5 patients (mean age 74·2 (4·8) years), all of whom had rest pain and four of whom faced amputation. All five occlusions were recanalised successfully without perforation using laser energy (mean total dose per occlusion—129 (34) J), and permitting subsequent balloon dilatation. The mean pretreatment Doppler ankle pressure index of 0·27 (0·12) increased to 0·5 (0·15) after treatment. In the two vessels with poor run off reocclusion occurred within 48 hours requiring below knee amputation. The other three patients have patent vessels, with abolition of rest pain and limb salvage.

Peripheral laser assisted balloon angioplasty with pulsed Nd-YAG laser energy and sapphire tipped fibres is safe and allows angioplasty to be performed when the balloon alone is unsuccessful.

Coronary angioplasty as a treatment for patients with angina pectoris after a non-Q wave myocardial infarction

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More aggressive treatment has been suggested for patients who sustain a non-Q wave myocardial infarction because of the subsequent unstable angina, recurrent myocardial infarction, and high mortality are common compared with patients with Q wave myocardial infarction. We therefore analysed the outcome of 116 patients who had coronary angioplasty (PTCA) after a non-Q wave myocardial infarction between 1981 and 1986. All patients were symptomatic, 47% having unstable angina before angioplasty, which was performed a median of 31 days after the infarction. Nineteen per cent of patients had a totally occluded vessel at the time of attempted PTCA and the primary success rate (less than 50% stenosis) of the procedure was 87%. A mean clinical follow up of 15 (range 3–59) months was obtained in all patients. Complications related to the angioplasty were emergency surgery in seven (6%) patients, and myocardial infarction in five (4%). Late recurrent myocardial infarction occurred in four (3%) patients and further revascularisation procedures were necessary in 19 (16%) patients who had a further PTCA, and five (4%) patients who had late coronary artery surgery. One patient died following operation after a failed PTCA. After a successful PTCA and if necessary a further PTCA, 73% of patients were asymptomatic and on no antianginal treatment at follow up.

In this selected group of patients with a non-Q wave myocardial infarction the high initial success rate, low incidence of subsequent death and recurrent myocardial infarction, together with sustained symptomatic benefit, suggest that PTCA is an effective treatment.

Predictors of restenosis after percutaneous transluminal coronary angioplasty

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The long term efficacy of percutaneous transluminal coronary angioplasty (PTCA) is limited by early restenosis which affects 20 to 30% of patients. There is therefore an important need to identify risk factors for restenosis. We have analysed 20 baseline variables in a cohort of 328 patients after successful PTCA followed up for at least six months. Clinical relapse defined by symptomatic or exercise test criteria occurred in 97 patients, all of whom underwent repeat arteriography. In total, arteriographic follow up was available in 126 patients and coronary restenosis of at least 50% luminal diameter was shown in 70 patients (21%). χ^2 testing identified emergency PTCA, residual stenosis, grade of angina, male sex, and positive predischarge stress test as significant ($p < 0.05$) univariate predictors of restenosis. Multivariate analysis was performed using stepwise logistic regression and restenosis risk ratios were calculated for each predictor variable (values in parentheses). Emergency PTCA (3·7), male sex (3·2), residual stenosis (2·4 for 30% stenosis), and positive predischarge stress test (2·1) were all retained as significant ($p < 0.05$) independent predictors of restenosis.

These data indicate that clinical relapse after successful PTCA is not always associated with coronary restenosis. Patients at greatest risk of restenosis are men undergoing emergency PTCA, particularly when the residual stenosis remains appreciable (30–50%). A positive predischarge stress test provides additional independently predictive data.

Sustained long term improvement in left ventricular function after successful coronary angioplasty

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Data on long term clinical efficacy of successful coronary angioplasty (PTCA) is now available. In order to evaluate the long term benefits in left ventricular (LV) function, 49 patients who had had rest and exercise Tc^{99m} gated blood pool images before and six weeks after successful PTCA were studied at a mean interval of 15 months (range 9–24) after the procedure. None of the patients had clinical evidence of restenosis; 15 (group A) had post infarction angina whereas the remaining 34 (group B) had no previous infarction. In both groups before PTCA there was a significant fall in ejection fraction on exercise more pronounced in group A (A 48% (10)–40% (16), $p < 0.001$; B 58% (10)–53 (13), $p < 0.005$). This change was paralleled by a worsening wall motion score (A 2·3 (1·9)–3·3 (2·4), $p < 0.01$; B 0·6 (0·4)–1·6 (1·2), $p < 0.001$). Six weeks after the procedure there was no significant change in resting ejection fraction but there was a significant increase on exercise, particularly in group A (A 53% (13), $p < 0{\cdot}001$; B 62% (11), $p < 0{\cdot}001$) with a concomitant improvement in exercise wall motion score (A 1·8(1·1), $p < 0{\cdot}005$; B 0·4(0·6), $p < 0{\cdot}001$). This improvement in exercise ejection fraction and wall motion was maintained at later follow up with no significant deterioration in either measurement and a clearly sustained significant improvement over pre-PTCA values for ejection fraction (A 51% (10), $p < 0{\cdot}005$; B 60% (10), $p < 0{\cdot}002$) and wall motion (A 1·3(0·8), $p < 0{\cdot}001$; B 0·2(0·2), $p < 0{\cdot}0001$).

Thus the immediate improvement in left ventricular function after successful PTCA is maintained in patients with and without previous myocardial infarct for up to two years.

Coronary angioplasty in unstable angina: higher success rate and lower complications than in stable angina

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Unstable angina is associated with plaque rupture, coronary artery spasm, and intravascular clot formation, suggesting that coronary angioplasty may not be the ideal form of treatment. We therefore examined the success and complication rates of percutaneous transluminal coronary angioplasty in unstable angina compared with stable angina. Two hundred patients (250 lesions) underwent coronary angioplasty from November 1982 to February 1987. The indication for angioplasty was unstable angina in 118 (59%) and stable angina in 69 (35%) (others included acute infarction and after streptokinase reperfusion). The mean age was 53 years, 162 were men and 38 women, and 112 (56%) had single vessel disease. The equipment, techniques, and drugs used were similar in stable and unstable angina. Primary success (at least 20% reduction in luminal stenosis without major complications) was achieved in 146 cases (73%) and 192 lesions (77%). Luminal stenosis was reduced from a mean of 87 (11)% to 27 (15)%. In patients with unstable angina the success rate (81%) was significantly higher than in those with stable angina (57%) $p < 0{\cdot}01$. Success rates were not significantly different between men and women, 73% and 71%, respectively. Similar success rates were achieved in each of the main coronary arteries: left anterior descending 132 of 176 (75%), right coronary 13 of 18 (72%), and circumflex seven of 12 (58%), NS.

Major complications (mortality, emergency coronary artery bypass grafting, or infarction) occurred in 12% of the whole group. In patients with stable angina major complications were significantly greater than in those with unstable angina, 22% versus 7·6%, $p < 0{\cdot}01$.

Systolic and diastolic blood pressures in prediction of heart attacks and stroke

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The relative importance of systolic and diastolic blood pressures in predicting risk and likely benefit from treatment remains controversial. The British Regional Heart Study provides data on 7735 middle aged men followed for cardiovascular events for six years; 336 of the men have had an MI, fatal or non-fatal, and 71 men have had strokes. Systolic and diastolic blood pressures are strongly correlated, $r = 0{\cdot}70$, but there is considerable discordance in the association. Their independent and combined ability to predict major cardiovascular events has therefore been examined. If diastolic blood pressure (DBP) is used as the basic measurement, an increment in systolic blood pressure (SBP) above the average figure associated with that DBP (for that age-group) increases the risk of a heart attack. Using SBP, a similar phenomenon is observed for increments in DBP, but the effect is less pronounced.

Our findings suggest that DBP should be used as the basic measure together with assessment of the systolic increment as a more precise guide to risk of ischaemic heart disease. For stroke, SBP appears to be paramount and increments in DBP above the average contribute no further risk. There are considerable implications in these observations for the design of clinical trials and for the management of raised blood pressure.

Variation in general practitioner referral for assessment of patients with chest pain: impact on need for coronary artery bypass grafting

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The need for invasive cardiological assessment and revascularisation procedures is related to the prevalence of coronary artery disease. It is also related to the resources available and to the perception by patients and their general practitioners (GPs) of the possible benefits. We have previously noted a wide variation in the numbers of patients referred by individual GPs in north west Surrey for investigation of chest pain. This study sought to elucidate this phenomenon. Between 1982–6, 441 patients were referred for coronary angiography, 316 subsequently undergoing CABG (219) or PTCA (26). These patients originated from 89 principals in general practice, of whom 13 were excluded on the grounds of death, retirement, recent appointment, or small intradistrict practice (< 1000 patients). The GPs were ranked by total number of patients undergoing coronary angiography followed by CABG or PTCA, and by number per 1000 patients on the practice list. There was a mean of 4·32 patients per GP, referred by the district cardiological unit for coronary angiography originating from the top decile of GPs over the five year period, and of 0 56 patients from the bottom decile. The distribution represented an exponential decline. The figures for the uptake of surgery were 3·26 patients/1000 practice list five years, and 0·38 patients/1000 practice list/five years, respectively. If the referral rate of the district was that of the top 50th (rather than the 10th) centile of GPs, the need for the procedures was increased by 35% to about 380 CABG per million population per annum (490 corrected for the low SMR in ICD 410–414). This difference cannot be accounted for in terms of GP years qualified (23·3 years and 20·5 years, respectively, $p = 0{\cdot}196$, NS), nor was there detectable difference in the population structure between practices. Nevertheless a questionnaire seeking attitudes to referral disclosed that chest pain is a common symptom in general practice.

Current estimates of the national need for revascularisation procedures may seriously understate the true need, which is dependent on the awareness of both patients and their primary health care physicians.

Need for cardiac catheterisation and coronary artery surgery: experience of a district in the north west region

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A six year study (1981–86) was undertaken of the experience of the Wigan district in the north west region of the need for invasive cardiological procedures. A similar study has been reported to the Society from Surrey. The catchment population is 310 000 with a larger than expected number of people in social classes IV and V and a standardised mortality ratio for ischaemic heart disease of 1:28. The district has a cardiologist with sessions for cardiac catheterisation at the Regional Cardiothoracic Centre, easy access to invasive cardiac procedures, a fully equipped non-invasive cardiac laboratory, and local follow up of cardiological and cardiac surgical patients by the cardiologist, and the regional cardiac surgeon. A total of 579 patients was referred for investigation of coronary artery disease, and 222 patients for valvar heart disease. There was a greater than fourfold increase in the number of patients investigated for coronary artery disease (116 procedures/million population/year in 1981 compared with 490 procedures/million population/year in 1986. There was little change, however, in the number of valvar heart disease referrals yearly, 120 procedures/million population/year being the average, much higher than the national average. Adjusting the Surrey figures to our district we estimate that we need 594 operations/million population/year for coronary artery disease, but in 1986 our figures were 343 operations/million population.

The reasons for this deficiency may well be lack of staff, (one cardiologist for a population of over 300 000), an inadequate number of referrals from general practitioners and physicians, poor finance, and public ignorance of modern methods of management of coronary artery disease.

Tentative localisation of the gene responsible for hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy is a major cause of a sudden cardiac death in the young. Our regional clinical study has shown a minimum prevalence of 3·2/100 000. Echocardiography has shown a large number of asymptomatic relatives such that the pedigree structure is compatible with a monogenic disorder inherited as an autosomal dominant with variable expression and occasional non-penetrance. The rapid recent advances in recombinant DNA technology make gene localisation feasible either by the candidate gene approach or by linkage mapping. We have assembled 10 families in whom the latter approach may be useful. We explain the techniques and request the cooperation of colleagues in order to identify further informative pedigrees. Preliminary studies have shown that the short arm of chromosome 6 is a likely site; reanalysis of seven published pedigrees, together with data from four of our own, has given a lod score of 3·04 at 12 cm from the major histocompatibility locus. This observation represents odds of 1000 to 1 in favour of the gene being close to the HLA locus.

Even using only affected cases the lod score of 1·7 is suggestive of linkage. If confirmed by DNA studies gene localisation will become feasible.

Effect of serial tournament squash games on some cardiovascular and metabolic measurements

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Metabolic changes have been proposed as a possible cause of sudden death occurring during and after playing squash. Such changes have been shown in relation to one match. There have been no studies, however, evaluating the cumulative metabolic response to repetitive tournament squash playing. We therefore compared the cardiovascular and metabolic responses to exercise, in repeated (three games) competitive squash, over a 48 hour period, in 10 men aged >45 years. Subjects were studied at rest before exercise, on completion of exercise, and five and 30 minutes later. The following were measured on each occasion: heart rate and rhythm, and plasma concentrations of potassium, magnesium, lactate, and free fatty acids. Aerobic and anaerobic fitness were assessed by exercise testing on a treadmill (V_{o2} max) and by ergometer. Statistical analysis was performed by Student's paired *t* test. Repeated squash was associated with a similar fall in mean (SEM) plasma potassium (3·84 (0·1) to 3·65 (0·1) and 4·05 (0·1) to 3·76 (0·1) mmol/l, respectively, higher mean plasma lactate (68·33 (12·54) and 31·7 (8·7) mmol/l, respectively, $p < 0·05$) as compared with a single match at the end of exercise. Five minutes after repeated squash mean serum free fatty acid concentrations were higher (1·63 (0·34) and 0·84 (0·16) meq/l, respectively, $p < 0·05$) as compared with a single match. The mean plasma magnesium concentration tended to fall after squash but there was no difference between repeated squash and a single match. Poorer anaerobic fitness was associated with greater increments in lactate.

We conclude that squash is associated with changes in potassium, lactate, and free fatty acid concentrations that may be arrhythmogenic, and repeated squash over a 48 hour period is associated with greater increments in free fatty acid and lactate concentrations.

Hypertensive left ventricular hypertrophy and strain: evidence for a myocardial structural abnormality

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Factors other than blood pressure contribute to the increased mortality in hypertensive patients with electrocardiographic left ventricular hypertrophy (LVH) and strain. A study was therefore undertaken to assess the degree of myocardial fibrosis as determined by echo amplitude analysis. A mathematical index of colour encoded pixel intensity was calculated in 24 normal subjects, 37 athletes with LVH, and 65 hypertensive patients with varying degrees of ECG abnormality (12 normal ECG, 16 ECG–LVH (voltage only), and 37 ECG–LVH and strain, of whom 19 had coronary arteriography (seven with coronary artery disease (CAD) and 12 with normal coronary arteries). The mean (SD) posterior wall echo amplitudes were similar in all groups (normals 20·3 (2·2), athletes 20·2 (3·7), hypertensives 21·09 (3·63). There were, however, significant differences in the septum, with LVH and strain patients having higher amplitudes (27·02 (8·6) than normal subjects (21·5 (3·6)), athletes (22·7 (3·42)), and hypertensive patients with a normal ECG (22·4 (2·9)) (all $p < 0·05$). These increases did not correlate with left ventricular mass ($r = 0·32$, NS) or the presence of CAD.

Echo amplitude analysis of the septum separates not only physiological from pathological hypertrophy but also hypertensive patients with LVH and strain from those with a normal ECG. As this abnormality is not specifically related to increased mass or CAD it may be an additional contributory factor to the known increased mortality in hypertensive patients with LVH and strain.

Nocturnal decrease in fibrinolysis is consistent with peak onset of myocardial infarction, sudden cardiac death, and stroke

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The frequency of onset of myocardial infarction, sudden cardiac death, and stroke exhibits a circadian variation with a peak during the morning hours. We determined the circadian variation of plasma fibrinolytic factors from three hourly venous samples taken from six healthy non-smoking volunteers aged 23 to 39 years over a typical 24 hour period of normal activity. The activities of tissue type plasminogen activator (tPA) and the fast acting plasminogen activator inhibitor (PAI) were assessed by amidolytic spectrophotometric assays. A pronounced and opposite circadian variation in tPA and PAI activities was observed. The curves were sinusoidal with a peak tPA activity of 787(391) mIU/ml (mean (SD)) and lowest PAI activity of 13 (9·7)% pooled plasma inhibition occurring at 1800 hours. The lowest tPA activity of 3·85 (5·6) mIU/ml coincided with a peak PAI activity of 178 (62)% at 0300 h. The timing of peaks and nadirs was consistent among individuals (SD = 1 h, best fit curve) and the differences between mean peak and nadir activities were significant for both tPA ($p < 0.005$) and for PAI ($p < 0.002$). Peak to nadir change, however, in tPA and PAI varied considerably from one subject to another (47·3 to 242 mIU/ml for tPA, 115 to 274% for PAI).

The occurrence of greatest fibrinolytic inhibition with lowest fibrinolytic activity in the early morning hours suggests that reduced endogenous fibrinolysis may be a possible mechanism contributing to the onset of thrombosis in acute myocardial infarction, sudden cardiac death, and stroke.

Risk factors in prediction of heart attacks in men with pre-existing ischaemic heart disease

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There are strong associations between serum total cholesterol, blood pressure, and cigarette smoking, and the incidence of heart attack. In survivors of myocardial infarction (MI) the role of these risk factors is apparently diminished. In the British Regional Heart Study in 6·2 years average follow up, 336 of the 7735 men have suffered a heart attack, fatal or non-fatal. Of the middle aged men 1968 (25%) had evidence of pre-existing ischaemic heart disease (IHD). The men were grouped into (a) no evidence of pre-existing IHD, (b) those with evidence of pre-existing IHD other than definite MI, and (c) definite previous MI. After standardisation for age, attack rates for IHD were determined for each of the three groups for varying levels of the risk factors. Cigarette smoking is strongly associated with attack rate in group (a). In groups (b) and (c) the relation persists but is reduced to borderline significance. For systolic blood pressure, the strong relationship with risk in group (a) is almost as strong in group (b), but disappears in group (c). For serum total cholesterol, the strong association with attack rate in group (a) diminishes through group (b) to group (c) but remains appreciable and highly significant.

This observation, together with the results from previous studies and trials, suggests that reduction of total serum cholesterol in men with evidence of IHD may be at least as important as the control of blood pressure and the cessation of smoking.

Serotonin antagonism prevents myocardial infarction and death from coronary artery disease

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Serotonin may be an important mediator in the process of coronary thrombosis. It is plentiful in platelets and is released in large quantities during coronary thrombosis. It mediates the initial platelet thrombosis and vessel spasm and amplifies the effects of other mediators. A serotonin antagonist should therefore be a potential inhibitor of the whole process of coronary occlusion. Thirty eight patients with critical arterial stenoses shown by coronary angiography were divided into a control (aspirin treated) group and a ketanserin (serotonin antagonist) treated group in an open trial. The treatment that the patients would normally have undergone anyway,—for example, angioplasty, or coronary artery bypass grafting—was allowed to proceed in the usual way with both groups. Allocation according to age and severity of disease was carried out by a non-clinician who did not know the patients. Controls: n = 19, age 67·1 (8·4), 13 men and six women, affected vessels: one (n = 2), two (n = 7), three (n = 9); unstable angina, n = 2, stable angina, n = 17; angioplasty, n = 3, CABG, n = 7. Treated: n = 19, age 64·4 (7·4), 17 men and two women, involved vessels: one (n = 2), two (n = 5), three (n = 11); unstable angina, n = 2, stable angina, n = 17; angioplasty, n = 2, CABG, n = 8. During the two year follow up period none of the patients treated with ketanserin have had any major ischaemic episodes; they are symptom free or in the case of those with stable angina they remain stable. There have been two deaths in the control group, two myocardial infarctions, two coronary artery bypass graft thromboses, and one thrombotic arterial occlusion at the site of angioplasty requiring CABG.

These results constitute a significantly better outcome in the treated group ($p < 0{\cdot}05$, χ^2 test). It seems unlikely that this can be accounted for on the basis of different sex distribution between the groups.

Pre-existing coronary stenoses in patients with first myocardial infarction are not necessarily severe

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The sudden, often unheralded, onset of symptoms in acute myocardial infarction suggests that pre-existing coronary stenoses susceptible to acute thrombosis in the infarct related artery may not necessarily be severe. We studied 60 consecutive patients aged 27–78 years within six hours of the onset of their first acute myocardial infarction by performing coronary arteriography before and after intracoronary thrombolytic treatment. We assessed previous symptoms and collateral vessel filling of the occluded infarct vessel before thrombolysis and measured the severity of residual coronary stenoses after successful thrombolytic recanalisation using computerised angiography. Recanalisation was achieved in 48 patients with a residual stenosis diameter obstruction of 58·1 (10·8)% (mean (SD)) and a minimum absolute lumen of 1·10 (0·3) mm diameter. A residual stenosis of <50% was present in 12 (25%) patients but none had collateral filling, between 50–75% in 34 (71%) patients of whom 12 had collateral filling ($p = 0{\cdot}04$), and between 75–100% in two (4%) of whom one had collateral filling. Collateral filling was present in six of the 12 (20%) patients who did not recanalise. The symptoms before presentation did not correlate with the severity of the residual infarct related stenoses after thrombolysis, and the presence of collateral filling was not related to the preceding symptoms.

Residual coronary stenoses after thrombolysis in patients with their first acute myocardial infarction are not necessarily severely obstructive. Mild residual stenoses are associated with no short term collateral filling of the occluded artery.

Endothelial integrity in human atherosclerotic coronary arteries

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In experimental atheroma induced by lipid feeding the interplay of endothelial damage with platelets and macrophages is important in early plaque growth. Because endothelial integrity cannot be studied in specimens from necropsy or endarterectomy it is uncertain whether similar endothelial damage occurs over human plaques. In transplantation the coronary arteries can be perfused instantly with glutaraldehyde giving ideal endothelial preservation, free from artefact, for scanning electron microscopy. The right coronary arteries of six patients undergoing transplantation were studied. In two the artery was angiographically normal, in one irregular in outline, and three had appreciable stenosis. None of the patients had raised concentrations of cholesterol and triglycerides. In four of the six arteries the endothelial surface showed widespread focal abnormalities ranging from adhesion and migration of monocytes to loss of individual endothelial cells. Larger areas of endothelial denudation with exposure of underlying collagen were also seen. Loss of endothelial cells was associated with accumulation of macrophages, on and deep to the surface, as well as adhesion of platelets to the exposed subendothelial tissue. Endothelial damage was not related specifically to stenotic segments.

The results suggest that some patients with coronary atheroma have widespread focal endothelial cell abnormalities and that human atheroma in this regard, even in normolipidaemic patients, is similar to animal models. The morphological abnormalities of endothelial cells may indicate a more widespread functional change including loss of endothelial derived relaxant factor and altered vasomotor responses.

Is the in-hospital course of women after a first myocardial infarction different from that in men?

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The course of myocardial infarction in women has not yet been fully elucidated and it has been suggested that their prognosis is worse than that of men.

We studied risk factors and the course in hospital in 337 women and 658 men admitted with a first myocardial infarction or episode of acute coronary insufficiency. Women were older than men ($p < 0{\cdot}01$) and smoked less ($p < 0{\cdot}0001$), but more were hypertensive ($p < 0{\cdot}05$) and mean serum cholesterol concentration was higher ($p < 0{\cdot}05$). Logistic regression analysis showed that these risk factor differences, with the exception of hypertension, were not due to the age difference between the sexes. Women were more likely to be admitted with acute coronary insufficiency ($p < 0{\cdot}05$), and this difference was attributable to the differing risk factor distribution between the sexes. Women with infarctions had a higher rate of complications ($p < 0{\cdot}0001$). Their death rate (12·6%) was significantly higher than that among men in whom it was 6·5% ($p = 0{\cdot}02$). When the confounding effect of age was removed using logistic regression, sex no longer correlated with complications in hospital (NS) or mortality (NS).

Although risk factor differences exist between the sexes, gender per se does not influence the course in hospital of a first episode of acute coronary heart disease. Previously reported differences may be due to the effect of confounding variables, notably age.

Intracoronary epoprostenol: effects on coronary artery calibre

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Epoprostenol (prostacyclin, PGI_2) is a prostaglandin with vasodilatory and platelet inhibitory properties and could, therefore, be of benefit during coronary artery angioplasty. The aim of this study was to assess both the safety and angiographic vasodilatory capacity of intracoronary (I/C) epoprostenol. Sixteen patients were studied. After coronary angiography, the view displaying the left epicardial coronary arteries (ECA) most clearly was selected as a control. I/C epoprostenol was then given and the angiogram repeated in the chosen view. This was repeated with a higher dose of epoprostenol and again following I/C isosorbide dinitrate (ISDN). All angiograms were coded and analysed blind. ECA calibre was measured from traced projections of the angiograms. Blood pressure, heart rate, and ECG were recorded throughout. The first two patients received epoprostenol infusions of 2·5 and 5·0 ng/kg/min to assess safety, and no untoward reactions occurred. The next 10 patients had epoprostenol infusions of 5·0 and 7·5 ng/kg/min followed by I/C ISDN. No haemodynamic disturbances occurred and ECA calibre did not change with epoprostenol [mean ECA diameter mm (SD): control 2·85 (0·62), 5·0 ng/kg 2·80 (0·61), 7·5 ng/kg 2·80 (0·54)), but did increase with ISDN (3 17(0 36)) ($p < 0{\cdot}02$). The last four patients had epoprostenol infusions of 7·5 and 10 ng/kg followed by I/C ISDN, and two patients became hypotensive. ECA calibre did not change significantly [control 3·5 (0·45), 7·5 ng/kg/2·96 (0·81), 10 ng/kg 3·45 (0 96), ISDN 3·20 (0·61)]. Eight patients developed tall T waves on the ECG during epoprostenol infusions but no arrhythmias occurred.

The results suggest that clinically tolerable doses of I/C epoprostenol are not potent dilators of the ECAs, and that this route of administration is unlikely to be of use during coronary angioplasty.

Does hyperventilation have any cardiac effect in patients with chest pain?

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Intermittent acute episodes of hyperventilation have been documented in patients with angina like chest pain and both atheromatous and normal coronary arteries. A direct cardiac effect has been suggested. Fourteen consecutive patients undergoing cardiac catheterisation were studied. Seven had coronary artery disease (CAD) and seven normal coronary arteries (NCA). Medication was withdrawn before the study. Atenolol 100 mg was given four hours before the study and temporary pacing started at 70 bpm in order to avoid the sympathomimetic effects of hyperventilation. All patients hyperventilated for three minutes and a respiratory alkalosis resulted: mean arterial pH 7·53; mean $Paco_2$ of 26 (4·6) mm Hg. Coronary sinus Pco_2 fell by a mean of 17 (4·8) mm Hg. Arterial – venous oxygen ($A-Vo_2$) content widened from 9·1 (1·2) to 10·1 (1·0) ($p < 0{\cdot}03$) in patients with CAD and myocardial oxygen extraction increased by 4·5%. In NCA patients $A-Vo_2$ content difference narrowed from 10·0 (2·1) to 8·6 (1·0) (NS) and oxygen extraction fell by 6·4%. Arterial lactate concentration increased in response to HV in all subjects, but CS lactate increased only in the CAD patients (0·63 (0·07) to 0·8 (0·7), $p < 0{\cdot}02$). dP/dt max was measured using a fibreoptic Camino catheter and increased significantly in all patients following HV; left ventricular end-diastolic pressure only rose significantly (13·7 (2·4) to 17·4 (2·0); p < 0·03) in the patients with CAD.

Thus coronary flow limitation may occur in response to hyperventilation in patients with CAD, and ventricular function may deteriorate.

Free radical production and neutrophil elastase in myocardial injury

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Animal models of myocardial infarction suggest that the neutrophil, by releasing oxygen derived free radicals and elastase, may potentiate myocardial damage. We measured plasma lipid peroxidation products (octadecadienoic acid) as a measure of free radical production, and plasma neutrophil elastase concentrations as a measure of neutrophil activation, in normal controls, patients with stable angina, and sequentially in patients with acute myocardial infarction, over 48 hrs. Thirty five controls (mean age 35, range 22–63 years), 20 patients with stable angina (mean age 60, range 42–72) and 15 patients with acute infarction (mean age 58 years, range 35–73, peak creatine kinase (CK) concentration 1791 (223) u/l). There was no difference in plasma octadecadienoic acid between controls (20·4 (1·15) µmol/l) and patients with angina (23·5 (2·19) µmol/l). Peak plasma octadecadienoic acid concentrations were significantly higher in patients with acute myocardial infarction (36·9 (3·33) µmol/l) compared with controls (p < 0·001) or those with angina (p < 0·01). There was no difference in plasma neutrophil elastase concentrations between controls (21·1 (1·91) ng/ml) and patients with angina (26·6 (2·04) ng/ml). Peak plasma elastase concentrations were significantly higher in patients with myocardial infarction (58·3 (8·67) ng/ml) compared with controls (p < 0·001) and patients with angina (p < 0·001). Peak concentrations of octadecadienoic acid occurred earlier after the onset of chest pain (13·2 (2·0) hours) compared with peak concentrations of elastase (23·3 (3·6) hours) (p < 0·02).

While oxygen derived free radicals could derive from myocyte destruction, the elastase indicates degranulation of the neutrophil and confirms early activation of the neutrophil in myocardial infarction.

A comparison of exercise training and β blockade on the chronotropic response to treadmill exercise in angina pectoris

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Twenty four patients with chronic stable angina were recruited and randomised into two groups. Both groups underwent three standard symptom limited exercise tests on a treadmill, the first for familiarisation purposes, the second to obtain baseline values, and the third after treatment with atenolol 100 mg daily for seven days. β blockers were stopped and group A started exercise training for 11 minutes daily at home with weekly hospital supervision (Canadian Airforce PBX programme). Both groups initially received nifedipine 10 mg three times a day and were followed up for a year at which time all tests were repeated. Atenolol produced a 44% improvement in mean treadmill time for group A which was significant (p = 0·01). This was accompanied by an improvement in workload from 6 to 8 metabolic equivalents. Exercise training produced a much greater increase in treadmill time of 91% (p = 0·0007), a workload of 10 metabolic equivalents. This was significantly better than atenolol (p = 0·04). The heart rate at rest and at each stage of the exercise test was reduced following training but the degree of reduction was less than that when taking atenolol. Atenolol resulted in a significant fall in mean maximum double product, however, (p = 0·0002) while training produced a significant increase in mean maximum double product (p = 0·04). A non-significant deterioration in all the above measurements was seen in the control group. Drug usage among the training group decreased markedly while in the control group two patients required coronary artery bypass grafting.

Exercise training therefore produced changes in exercise tolerance superior to that achieved by β blockade.

Determinants of cerebral blood flow during cardiopulmonary bypass

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In a study of the cerebral consequences of cardiopulmonary bypass (CPB) we have assessed the cerebral blood flow (CBF) by intra-arterial Xenon-133 clearance, using a Novocerebrograph 10a, before, during, and immediately after CPB. All 51 patients under the care of a single surgical team had elective coronary revascularisation by a standardised anaesthetic and surgical protocol. CBF fell significantly from before (median 22) to on bypass (median 20) (Wilcoxon, $p < 0{\cdot}005$) and was significantly higher immediately after the bypass period (median 28) than before bypass (Wilcoxon, $p < 0{\cdot}001$). Scattergrams showed that CBF was independent of arterial pressure (BP) but was related to arterial carbon dioxide. The correlations between arterial carbon dioxide pressure and CBF before bypass ($r = 0{\cdot}46$, $p < 0{\cdot}001$) and after bypass ($r = 0{\cdot}46$, $p < 0{\cdot}002$) are very similar; while on bypass the correlation, although significant, is reduced. The median values for arterial carbon dioxide pressure were low throughout the study (before bypass, median 33; on bypass, median 28; and after bypass, median 36).

The maintenance of arterial carbon dioxide pressure within the normal range of 35–45 mm Hg may minimise the risk of low CBF caused by hypocarbia which could theoretically be harmful in patients known to be at risk of both short and long term cerebral dysfunction.

Long term evaluation of isolated Björk-Shiley mitral valve replacement

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Between 1973 and 1985, 331 patients out of 356 survived isolated mitral valve replacement with Björk-Shiley valves (models MBRP—standard, MBRC—convex-concave and MMSM—monostrut). We followed up 292 (88%) patients for up to 13 years, a total of 6620 patient-years, to determine the long term performance characteristics of these prostheses. At operation the mean age of the patients was 54 years (range 18–80), 70% were women, and 59% were in atrial fibrillation. The mitral valve disease was rheumatic in 132 (40%) and associated with endocarditis in 45 (14%) patients. The early mortality was 5% and there were 54 late deaths (19%; 0·8% per patient-year) of whom 35 (12%) were cardiac in origin with seven cases (2%) of thromboembolism of the valve. Total 13 year valve related morbidity in 48 patients (16%), 0·7% per patient-year) was due to thromboembolism in 29 (10%), prosthetic endocarditis in eight (3%), anticoagulant related haemorrhage in five (2%), and paraprosthetic regurgitation in six (2%). Reoperation was performed in five (2%) because of prosthetic endocarditis (three patients, 1%) or paraprosthetic regurgitation (two patients, 0·7%), all necessary within the first year after operation. No case of haemolysis or mechanical valve failure was recorded. Total 13 year actuarial estimates of survival were 58% and freedom from valve related morbidity 71%.

The Björk-Shiley models MBRP, MBRC, and MMSM mitral valve prostheses show satisfactory durability without any mechanical failure over a 13 year period. The long term outcome of isolated mitral valve replacement with these models is associated with a low incidence of valve related complications.

Conservative operations for congenital abnormalities of the mitral valve

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In congenital abnormalities of the mitral valve (MV), repair is the goal of surgical management. Between 1975 and 1987 10 patients aged between four months and 14 years (mean 56 months) underwent 11 operations, and follow up was both clinical and by cross sectional and Doppler echocardiography. Two children had isolated mitral incompetence, each with a giant left atrium causing airway obstruction and pulmonary complications; both valves were repaired (pericardial patch advancement of posterior cusp, repair of cleft anterior leaflet, annuloplasty, and enhancement of the commissural coaption). After seven and five years, respectively, both are well, free of murmurs, and have normal heart size and lung fields. Seven children had mitral stenosis (MS); six had supravalvar rings (SVR) and one had a parachute valve. Five had "forme fruste" of the Shone complex, each showing either two or three of its four features. Conservative operations were successful in six cases and mitral valve replacement (MVR), was required in one patient with SVR leading to the only operative death in this series. Associated procedures for subaortic stenosis were carried out in three patients. Of the six survivors one is abroad and lost to follow up and one required MVR five years later. After two to 138 months (mean 49 months) of follow up four are in grade I and one in grade II New York Heart Association classification; three have soft systolic murmurs, one has cardiomegaly, and valve thickening on Doppler. The final patient had redundant mitral tissue on the anterior leaflet which filled in systole and caused subaortic obstruction. This tissue was excised and the valve repaired, and the patient remains well and asymptomatic.

Conservative surgery was possible and had a good outcome in nine out of 10 cases with severe congenital MV anomalies.

Initial experience with seeding of a neointima in a rough surface left ventricular assist device

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Development of an implantable left ventricular assist device (LVAD) for prolonged circulatory support has been impeded by the lack of a suitable biomaterial to interface with circulating blood. Progressive thrombus formation has been noted on the surface of LVADs lined with smooth non-thrombogenic polymers designed to attract a fibrin coagulum. The Thermedics pneumatic LVAD has a rough surface lining made of an artificial collagen like matrix Biomer. Calf foetal fibroblasts in cell culture have previously been shown to proliferate and produce collagen freely. Three LVADs were seeded with a mean of 59 million of these cells before insertion into three month old calves, mean weight 76 kg. These devices were inserted for six hours, nine days, and three months. Histological and electron microscopic examination confirmed the presence of a smooth neointima containing two layers of viable active fibroblasts immersed in collagen and coagulum on the dynamic pusher plate surface of the LVAD. The seeded fibroblasts seem to have rapidly encouraged the laying down and adherence of this smooth neointima. Initially the static metal housing was covered with a thin layer of coagulum with no visible active fibroblasts. Consequently, our seeding technique included an initial prime with autologous plasma to improve fibroblast adhesion. Microscopic examination has confirmed this. There has been no thrombus formation observed within the retrieved LVADs, neither has there been any evidence of systemic micro or macro embolisation at necropsy.

This lining offers the potential for prolonging the thromboembolic free function of LVADs.

Association between coronary artery collateral circulation and post infarction ventricular septal defect

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Ventricular septal defect (VSD) after myocardial infarction (MI) was seen in 28 patients over four years. The mean age (67 years) and male/female ratio (1·3 : 1) differed from that usually associated with MI. Most patients (24 of 28) presented within 14 days of MI after a stable interval. All had heart failure and most (24) were hypotensive. Inotropic drugs were used in 21 and aortic balloon counterpulsation in 16. The angiographic features for these 28 VSD patients were compared with 123 stable patients also studied early after MI. The VSD group had strikingly fewer major collaterals to the infarct related artery (4% and 63% respectively, $p<0·01$) although minor collaterals occurred equally (18% and 15%) Total occlusion of the infarct vessel was seen in 23 (82%) and aneurysm formation in 17(67%). Additional coronary disease (stenosis >70%) was seen in 17 but only 10 had aortocoronary grafts (eight to a single vessel). Of 27 patients undergoing surgery eight had multiple VSDs, 17 patch repairs, 15 aneurysm resection, and two required reoperation. Overall mortality was 25% with one preoperative death, four perioperative deaths (one after reoperation), and two sudden deaths, one at three and one at seven months. Of the survivors 16 are well, four have symptomatic heart failure, one has dementia, and none has angina.

We conclude that a lack of collaterals to the infarct vessel suggests that a different balance of coronary circulation may pre-exist in older patients who have developed a VSD from other survivors of MI. Early operation with a low rate of grafting of non-infarct vessels gave a relatively low mortality.

Internal mammary artery grafting increases the incidence of shoulder girdle pain after cardiac surgery

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Exposure of the heart through median sternotomy requires distortion of the chest wall and shoulder girdle. The increased popularity of the internal mammary graft (IMA) and in particular the use of the Favorolo retractor may have added to the frequency of shoulder pain. We prospectively studied 53 patients undergoing cardiac surgery (17 coronary surgery with IMA, 14 without, 15 valve replacements, and seven other combinations) all free of shoulder pain before operation. All patients were examined six weeks after operation and most were followed up with clinical examination (21) or questionnaire (29) at six months. Pain of cardiac and pulmonary origin was excluded on clinical grounds. Shoulder symptoms were reported by 29 patients, 13 of 17 in the IMA group and 16 of 36 of the others ($p = 0{\cdot}02$, Fisher's exact test). The operative detail was not known at the time of evaluation. A specific diagnosis referrable to the shoulder girdle was made in six patients (two had shoulder capsulitis, two had supraspinatus tendonitis, and one had acromioclavicular and one sternoclavicular strain) and was of non-specific origin in the remaining 23. Pain started within three months of operation in 23 patients, lasted four to six months in 11 patients and interfered with activities of daily living in 13 (seven IMA, six others (NS, Fisher's exact test)). Four patients required physiotherapy or intra-articular injections.

Accurate diagnosis of the source of pain may lead to specific treatment. Awareness of the problem should reduce unnecessary or excessive retraction.

Initial trials of a transtelephonic defibrillator

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For patients with out of hospital ventricular fibrillation, the time until attempted defibrillation is one of the major determinants of survival. Earlier defibrillation can be facilitated by remote telephonic control of a defibrillator placed in the patient's home. We have assessed the efficacy of transtelephonic defibrillation (TTD) in 26 cardioversions (CV) (25 elective, one emergency) of atrial fibrillation ($n = 22$), and ventricular tachycardia ($n = 4$) performed in 23 patients (16 men, seven women) aged 46–81 (mean 61 years). The patient unit (PU) contains a microprocessor, microphone, defibrillator, and ECG/defibrillator pads applied to the patient's chest. The PU is connected to a standard telephone and once activated automatically dials and activates the remotely sited base station (BS) establishing ECG transmission and two way voice communication. The physician at the BS diagnoses the rhythm and controls defibrillator synchronisation, charging, and discharge, having confirmed anaesthesia. Accuracy of the ECG/defibrillator pad position is assessed by monitoring of transthoracic impedance at the BS. The time for activation of the BS by the PU ranged from 18 to 24 seconds (mean 20·5), and in all CV clear voice communication and ECG signals were established. A total of 75 DC shocks (50–360 J) were safely administered with no adverse effects and were successful in 24 of 26 CV. The average discharge delay time from BS to PU was 2·6 seconds (range 1 5–5).

TTD has the potential for more rapid defibrillation of patients with ventricular fibrillation and minimises patients' or spouses' interaction with the system.

Surgery for "inoperable" ventricular tachycardia

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Intraoperative arrhythmia activation mapping underlies the impressive success of surgery for sustained uniform ventricular tachycardia. Unstable arrhythmias and those intraoperatively non-inducible, however, are not amenable to activation mapping and have been considered "inoperable". We propose that fragmentation mapping in sinus rhythm can direct surgery in such arrhythmias. In 18 of 51 patients operated at this unit, intraoperative arrhythmia mapping was impossible because of non-inducibility ($n = 15$) or unstable configuration ($n = 3$). Surgery comprised endocardial resection of all areas showing fragmented local electrograms in sinus rhythm (> 100 ms duration). Mean patient characteristics included: age 52 years; arrhythmic episodes 18 (range 2–200); antiarrhythmic drug failures 4; left ventricular ejection fraction 33%. There were five (28%) early postoperative deaths (heart failure, three; sudden, one; metabolic, one) and one early recurrence of arrhythmia. There have been two late non-arrhythmic deaths and no further arrhythmia recurrences with mean follow up of 22(19) months. No patient requires long term antiarrhythmic drug treatment.

Fragmentation mapping successfully extends the surgical option to arrhythmias previously considered "inoperable" with results that compare favourably with those for arrhythmias in which operation was directed by activation mapping.

Surgical correction of atrioventricular junction reentrant tachycardia

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It has been assumed that the reentry circuit in atrioventricular junction reentrant tachycardia (AVJRT) is entirely intranodal. It has recently been proposed, however, that extranodal atrial fibres may form part of the reentry circuit and that surgical division of these fibres will abolish AVJRT while preserving A–V conduction. We have performed this operation on eight patients, three men, mean age 21·8 (range 13–34) years, with recurrent AVJRT. At preoperative electrophysiology study AVJRT was classified as type A: earliest atrial activation recorded by the His catheter (seven patients) and type B: earliest activation recorded in the proximal coronary sinus (one patient). Four patients also had A–V accessory pathways (AP). All patients underwent A–V nodal dissection—anterior for type A and posterior for type B including map-guided division of AP also where appropriate. All APs were successfully divided. V–A conduction was abolished in five patients. One patient had long term A–V dissociation requiring a permanent pacemaker. A–V conduction was preserved in the remainder but was apparently modified in most. Only one patient (BS) had a recurrence of AVJRT. In this patient AVJRT continued despite complete atrial dissociation during tachycardia implying an entirely intranodal circuit. AVJRT could not be induced in any of the other patients at a postoperative electrophysiological study.

These results confirm that this operation can abolish AVJRT without destroying A–V conduction. The findings in BS suggest, however, that its success is caused by modification of intranodal conduction rather than division of a specific extranodal pathway.

Concealed pre-excitation does not protect against rapid ventricular response to atrial fibrillation

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The Wolff-Parkinson-White syndrome has a typical electrocardiographic appearance. When pre-excitation is intermittent, or disappears during exercise testing or other manoeuvres, the risk of a rapid ventricular response to atrial fibrillation is thought to be low. The discovery of unsuspected accessory pathways in several reports on sudden cardiac death suggests otherwise. Among 108 patients with pre-excitation we have identified three in whom anterograde conduction across the accessory pathway was evident only with atrial pacing or with development of atrial fibrillation. One patient presented with near syncope and the others with palpitations. All had normal electrocardiograms in sinus rhythm. Although re-entrant atrioventricular tachycardia was the initial arrhythmia in one, the others had presented with atrial fibrillation with complexes suggesting pre-excitation. At electrophysiological study incremental right atrial pacing confirmed the presence in all of an accessory pathway which was located on the left side. The range of mean ventricular responses during induced atrial fibrillation was 200–280/minute. One patient had enhanced atrioventricular nodal conduction, and one also had mitral valve disease with an enlarged left atrium.

Atrial fibrillation may be responsible for exposure of obvious pre-excitation on the surface electrocardiogram even when this is not visible in sinus rhythm. Important contributing factors to this may be the location of the pathway, the rapidity of atrioventricular nodal conduction, and atrial disease. The absence of resting pre-excitation does not exclude the possibility of dangerously high ventricular rates.

d-Sotalol-induced infra-His block: evidence of class III activity

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d-Sotalol prolongs action potential duration, and has effects consistent with class III activity, prolonging atrial and ventricular refractoriness. Its effect on the His-Purkinje system is not known. To study this, measurements of AV nodal and His-Purkinje function were made before and after intravenous infusion of d-sotalol 1–2 mg/kg) in 16 patients. The AH interval increased from 100(32) to 113(34) ms ($p<0{\cdot}05$). The AV nodal effective and functional refractory periods prolonged from 342(65) to 391(85) ms ($p<0{\cdot}01$) and from 429(74) to 465(87) ms ($p<0{\cdot}01$). The functional refractory period of the His-Purkinje system was prolonged from 429(71) to 471(85) ms ($p<0\ 001$). The HV interval at rest did not change (49(11) to 53(12) ms, NS) but HV prolongation was shown after either atrial extrasystoles or by rapid atrial pacing, after but not before d-sotalol infusion in six patients. Second degree infra-hisian block was shown in four patients, only after d-sotalol infusion.

d-sotalol therefore has pronounced effects on the His-Purkinje system, increasing refractoriness in all 16 patients and causing infra-hisian block in 4 of 16. Similar effects have also been observed during amiodarone treatment, suggesting that prolongation of His-Purkinje refractoriness and infra-hisian block may be markers of class III activity.

Formation, transmission, and importance of high pressure shock waves during catheter ablation

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High pressure waves after catheter ablation shocks have been suggested as both partially therapeutic and potentially damaging. We investigated shock wave formation by delivery of high energy discharges in a saline tank, with voltage, current, and photographic recording, and high pressure, high frequency manometry. Standard defibrillator impulses arced above 10 J (cathodal) and 15 J (anodal). Arcing was always associated with rapid gas production near the electrode and transient reduction in current flow. Peak pressure increased linearly with energy above this threshold. The slope was greater for anodal pulses, and thus very high energy (>200 J) anodal discharges produced the greater shock wave. Peak pressure at 5 cm was 5 atm for a 200 J cathodal or anodal shock, and decreased linearly with the inverse of distance from the electrode. Mean propagation velocity was 1594(14) m/s. Perspex and tissue barriers were introduced between electrode and transducer. Perspex completely absorbed the shock wave, but tissue barriers up to 15 mm thick did not attenuate the shock. Thus shock wave energy is not absorbed by tissue, and direct barotrauma cannot occur. All shock waves had a secondary negative pressure wave, however, which induced gaseous microbubbles by cavitation. The collapse of these bubbles may contribute to diffuse myocardial damage, while rupture of myocardial structures is probably due to localised rapid gas production. Using a new energy source and catheter, four ablations (2 His bundle, 2 VT) have been successfully carried out in man without arcing (individual shock energies 2-40 J).

Direct barotrauma does not appear to exist, and secondary mechanical damage, while potentially relevant for unwanted side effects, is unnecessary for therapeutic ablation. A new completely non-arcing system may greatly increase safety margins in ablation.

Silent myocardial ischaemia after myocardial infarction: incidence and importance

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The incidence and importance of silent ischaemia after myocardial infarction (MI) is not clear. We defined silent ischaemia as asymptomatic ST segment depression on a submaximal exercise test (SMET). Patients studied were consecutive stable survivors of MI who had an early SMET and were followed up for one year. There were 67 patients with silent ischaemia (group I), 37 with angina and ST depression (group II), and 123 with a negative SMET (group III). The mortality in groups I (9%) and II (11%) were similar, and significantly higher than in group III (0·9% $p<0·005$). Groups I and II did not differ in the extent of coronary disease, the degree of collateral circulation to the infarct related vessel, the severity of left ventricular damage, or the rate of further MI. Fewer group I patients had Q wave infarction and fewer complained of angina or underwent coronary artery surgery in the first year. The frequency of further MI or angina was similar in groups I and III. More group I patients had inferior MI and more had coronary artery surgery. Half the excess mortality in group I over III was due to sudden death (three of six).

We conclude that silent ischaemia occurs often in stable patients after MI (>25%) and carries an increased mortality over patients without ischaemic changes on SMET.

Frequency and characteristics of silent ischaemia in patients with coronary artery disease

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We studied 112 unselected patients (88 men), mean age 55 (range 35–75) with documented coronary artery disease (37 one vessel disease, 24 two vessel disease, 51 three vessel disease) using exercise electrocardiography and ambulatory ST segment Holter monitoring. Patients underwent 24–48 hours (total 4721) of ambulatory monitoring off all anti-anginal treatment. Seventy one patients had a total of 454 episodes of ST segment change (342 painless, 112 painful) during monitoring. Eleven had only painful episodes, 25 only painless, and 34 had both. Forty two patients had no ST changes. Episodes of silent ST segment change occurred throughout the day, but predominantly between 7 am and 8 pm, with a peak between 12 noon and 1 pm. There was no association between total or silent episodes of ST segment change and severity of coronary artery disease. Silent episodes were most frequent in patients with exercise tests positive at a low work load (<6 minutes); those who developed ST segment depression at high work loads (>9 minutes) rarely had silent ST segment changes on ambulatory monitoring. The mean number of all episodes of ST segment change per patient per day was 2·31 (1·74 silent); only 11 patients, however, (10%) had 49% of all episodes recorded, and 32 (29%) had 82%. For silent ischaemia, 11 patients (10%) had 54% of episodes, and 39 patients (35%) had 93%.

Of all episodes of ST segment change on Holter monitoring in patients with coronary artery disease 75% are silent and occur particularly in those with a definitely positive exercise test. Fifty three patients (47%) had no evidence of silent ST change, and only 25 (22%) had silent ST changes alone on Holter monitoring. It cannot therefore be concluded that most patients with ischaemic heart disease have frequent silent ischaemia, as has been previously assumed.

Prognostic implications of silent ischaemia on exercise testing after myocardial infarction

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The frequency and prognostic implications of silent ischaemia were investigated in 359 survivors of myocardial infarction. Predischarge exercise testing was performed following a modified Bruce protocol. Silent ischaemia was defined as the presence of $\geq 0\cdot1$ mV horizontal or downsloping ST depression during the exercise test, in the absence of chest pain. Patients were followed up for 12 months. Exercise tests were negative in 152 patients (42%) (group 1); silent ischaemia was observed in 103 patients (29%) (group 2), and painful ischaemia observed in 82 patients (23%) (group 3). The mortality in the first year was lowest in group 1 (2%), 4% in group 2, and 8% in group 3, with reinfarction rates of 3%, 8%, and 18%, respectively. The likelihood of subsequently developing angina was 16% (group 1) compared with 47% (group 2), ($p<0\cdot001$). These results indicate that silent ischaemia on exercise testing in survivors of acute myocardial infarction was common, being seen in 29% of patients.

Silent ischaemia defined in this way conferred an intermediate risk of subsequent cardiac events compared with those with a negative predischarge exercise test and those displaying painful ischaemia. In addition, silent ischaemia was a strong predictor of subsequent angina pectoris.

Contraction/excitation feedback in man?

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Myocardial length/tension has been shown to influence repolarisation time and refractoriness in animals (contraction/excitation feedback) but, as yet, this has not been shown in man. During cardiopulmonary bypass the ventricle is in a relaxed, nonworking state with a systolic pressure of less than 50 mm Hg. Pressure is progressively increased over a period of about one minute as bypass is discontinued. A unique opportunity exists therefore to provide a clinical correlate for this feedback mechanism. Monophasic action potentials (MAPs) were recorded from the left ventricular epicardial surface as a measure of repolarisation time using a hand held pressure contact electrode. Arterial systolic pressure (radial cannula) was used as an indirect measure of LV systolic pressure. Measurements were made in 16 patients after routine coronary artery surgery. MAP duration shortened as systolic pressure increased. At 90% repolarisation MAP duration shortened from 288 0 ms (SD 29·5) at the onset of LV ejection on bypass to 261·0 ms (28·8) ($p<0\cdot001$) at completion of coming off bypass. Systolic pressure increased from 54·1 mm Hg (9·3) on bypass to 75·5 mm Hg (13·3) ($p<0\cdot001$) at completion. Regression analysis showed a strong correlation between MAP duration and systolic pressure ($p<0\cdot001$).

These results are consistent with the existence of contraction/excitation feedback in man. Such a mechanism may relate to the association of arrhythmias with asynergic wall motion by the creation of local inhomogeneous repolarisation times.

Continuous electrocardiographic monitoring in male veteran endurance athletes

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The short term benefits of exercise are established. The long term effects of endurance exercise on cardiac function have not so far been assessed. Twenty male veteran endurance athletes were studied to establish the effect of chronic exercise and were compared with matched controls. The mean age of the athletes was 54 years, all had run at least 30 miles each week for at least 25 years. Forty eight hour continuous electrocardiography showed mean heart rate of 59 bpm in athletes compared with 74 bpm in controls ($p<0\cdot001$). Minimum heart rate in athletes was 37 bpm compared to 47 bpm in controls ($p<0\cdot001$). Circadian variation in heart rate was maintained. Fifteen out of 20 athletes had at least one ventricular extrasystole. Only four out of 20 had more than 50 extrasystoles per 24 hours. One athlete had in excess of 1600 extrasystoles in 24 hours, four athletes had complex forms. This was compared with 18 out of 20 controls who had PVCs, only four of whom had more than 50 in 24 hours but two of whom had evidence of SVT. There was no significant difference between the groups. Eight out of 20 athletes but only two out of 20 controls had periods of asystole ranging in length from 1·5–12 seconds, occurring in 846 occasions in the athletes and only four occasions in the controls. Two subjects had AV block, both of them exhibited first, second, and third degree heart block, and one required permanent pacemaker implantation.

Continuous running throughout life results in lower heart rates and greatly increased prevalence of asystolic pauses and AV node dysfunction. There is no difference in ectopic activity between athletes and controls.

ECG analysis by computer and cardiologist: a multicentre cooperative study

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A large multicentre evaluation of the use of computers for ECG analysis has been in progress with the support of the European Economic Community (EEC) during the past few years. The pilot diagnostic phase of the study has now been reached whereby the accuracy of 11 programs (including many commercially available) and six cardiologists has been assessed against a well defined clinical data base of 250 patients. The clinical diagnoses based on echocardiography and coronary arteriography, for example, consisted of seven mutually exclusive groups: normal, LVH, RVH, BVH, anterior, inferior, and combined myocardial infarction. Rhythm analysis and other ECG dependent diagnoses, (for example, conduction defects) were not included. The 250 ECGs were analysed in different centres in Europe (including Glasgow), North America, and Japan. The six European cardiologists interpreted the ECGs independently. All reports were sent to the coordinating centre in Belgium for statistical analysis. The highest total accuracy of the computer programs was 76% (Glasgow Program) and the highest total accuracy of an individual cardiologist was 78%. There was a wide variation among programs and cardiologists not only in total accuracy but within individual diagnostic groups. BVH as well as multiple infarcts were analysed poorly by programs and cardiologists. The programs were superior in detecting LVH but the cardiologists were better in reporting single infarcts. Predictive values were similar for programs and physicians.

The results of this preliminary study indicate that the Glasgow computer program is as accurate as cardiologists in interpreting an ECG when each is measured against clinical data.

Computerised manikin for advanced resuscitation training

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Advanced cardiac life support requires practical skills additional to basic cardiopulmonary resuscitation including the use of airway adjuncts, endotracheal intubation, arrhythmia recognition, defibrillation, and intravenous access (peripheral and central). These activities need to be learned in an integrated and coordinated manner but no single manikin presently available can support this range of skills. A new computerised simulator capable of independent "life like" cardiorespiratory function is presented. The full length manikin supports basic and advanced cardiopulmonary resuscitation and is controlled by an Apple microcomputer which generates a range of ECG rhythms with appropriate stroke volume and blood pressure (BP) and palpable carotid pulse. Variable ventilatory rates and volumes are generated by a pump which provides realistic chest movements. Pupillary constriction and the achievement of an adequate supply of oxygen to the brain are indices of cerebral wellbeing. The ECG signal can be monitored from chest electrodes while a safe mock defibrillator with optional "quick look" paddles is used to teach defibrillation or synchronised countershock. Correct performance provides rhythm change and a realistic body jerk. One video display of graphics provides a two to three minute bar trend recording of BP, respiratory volume, brain oxygen, and textual comment. A second page shows a display of the real time ECG and analogue waveforms.

This manikin permits team training under realistic conditions. It simulates a range of clinical problems and measures response and quantifies performance in an objective and practical manner.

Evaluation of an advanced resuscitation training course for preregistration house officers

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Preregistration doctors in the "cardiac arrest" team need skills and knowledge of basic resuscitation and advanced cardiac life support (ACLS). A course was designed following the recommendations of the Resuscitation Council (UK) and a simplified version of the American Heart Association ACLS programme. The subjects were 60 newly qualified doctors who were assessed in two consecutive groups. As undergraduates they had been trained in basic resuscitation. Group 1 ($n=31$) (starting their first job) were pretested and taught ACLS in two 2 hour sessions, and after five months retested to measure their skills. Group 2 ($n=29$) had worked at other hospitals for six months but received no resuscitation training. They were taught and tested in the same way as group 1 at the beginning of their second post. At each session they completed questionnaires on their ability to perform resuscitation. In both groups the mean scores on knowledge and skill of resuscitation were significantly greater immediately after training. The knowledge and skills of group 1 five months after training were significantly greater than pretraining ($p<0{\cdot}001$) but slightly worse than immediately after training ($p<0{\cdot}01$). The more cardiac arrests the subjects attended, the more confident they felt in their ability to perform resuscitation; this was not matched by increasing competence. Five months after training there was a significant positive correlation between expressed confidence at performing resuscitation and demonstrated skill.

This study showed that the high degree of knowledge and skill acquired during the ACLS course were subject only to modest decay. Experience gave rise to false confidence and is not a substitute for training.

Electrode pad size and defibrillation success

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Although electrode size is an important determinant of current flow during countershock, larger pads have not been shown to be associated with increased defibrillation success in humans. To assess the effect of increasing the size of self adhesive ECG/defibrillator pads on the success of defibrillation we studied 123 cardiac arrests (CA) due to primary ventricular fibrillation (PVF) in 105 patients (31 men, 74 women) aged 40–84 (mean 64 years). Transthoracic impedance (TTI) was measured before defibrillation using a 30 kHz current passed through the chest via the ECG/defibrillator pads applied anteroanteriorly. We have previously shown that this method accurately predicts the actual impedance to a discharge. Pad diameters were small (8 cm/8 cm) in 26 CA, intermediate (8 cm/12 cm) in 63 CA, and large (12 cm/12 cm) in 34 CA. Mean(SD) TTI decreased with increasing pad size (112·2Ω(17) vs 92 3(22) and 71·6(14), respectively, ($p=0\ 0001$). Only the first episode of PVF during CA was analysed. A single shock of 200 J (delivered energy) was successful in 8 of 26 (31%) CA with small pads, 40 of 63 (63%) with intermediate pads, and 28 of 34 (82%) with large pads, $p=0{\cdot}0003$. A second 200 J shock increased the cumulative defibrillation rates to 12 of 26 (46%), 50 of 63 (79%), and 33 of 34 (97%) respectively, $p<0{\cdot}0001$.

In PVF larger self adhesive ECG/defibrillator pads are associated with reduced TTI and improved success rates for defibrillation with low energy shocks.

Patient delay in acute myocardial infarction

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The longest component of the total delay in coming under coronary care is patient delay, and it has been suggested that public education might be successful in making it shorter. We have studied the patterns of patient delay and their association with late mortality in 450 patients with acute myocardial infarction uncomplicated by cardiac arrest, of whom 243 had a previous history of ischaemic heart disease. Patient delays showed a skewed distribution with a modal delay of up to 1 hour, a median delay of 2 hours, and a mean delay of 10 hours. Two thirds of patients had sought help within four hours of the onset of symptoms. During the first four hours the longer patients delayed the lower subsequent mortality (27%, 18%, and 9% for 0 to one, one to two, and over two to four hours, respectively). One explanation may be that those with larger infarcts call sooner. Patients who presented after four to eight hours, however, had the highest mortality of all (38%), perhaps because such patients had developed serious complications of infarction. The pattern of patient delays was not altered by a previous history of ischaemic heart disease, with 69% and 68% of patients with and without a previous history of delaying up to four hours.

These findings suggest that the patient's call for help may be an instinctive pattern of behaviour which may therefore be difficult to modify by public education. Nevertheless a higher proportion of patients was seen early after infarction than in recent trials of thrombolytic treatment.

Direct admission to the coronary care unit with a telephone link system increases the number of patients suitable for thrombolytic treatment

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A narrow time window for administration of thrombolytic treatment in patients with acute myocardial infarction (AMI) makes it necessary to reduce to a minimum the delay in admission to the coronary care unit (CCU). While it is difficult to reduce the delay encountered in reporting of symptoms, avoidable delay has been identified in admitting the patients via the casualty department and GPs have also commented on the delay in the response of hospital switchboards to incoming calls. We have therefore looked firstly at the effect of a direct "back door" admission policy to CCU in reducing the delay, and secondly at the combination of this admission policy plus the use of a telephone line which bypassed the hospital switchboard. A total of 95 patients were included in the study of whom 48% were subsequently shown to have had an AMI. In the first study the time from arrival of the GP at the patient's home until admission to the CCU was reduced from 88(30) minutes to 65(29) minutes ($p<0.05$) and in the second study a direct admission policy plus telephone link reduced the delay from 90(51) minutes to 35(13) minutes ($p<0.001$).

These combined measures increased by twofold the number of patients admitted within a three hour time window from onset of symptoms and therefore increased the number of patients suitable for and likely to benefit from thrombolytic treatment.

Risk factors and in hospital outcome of a first myocardial infarction in the elderly

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The elderly form an increasingly large proportion of those admitted to the coronary care unit (CCU). Of a total of 980 patients, 53% were aged over 60, and 24% over 70 years; they were studied to examine age-related differences in risk factors, in-hospital complications, and mortality. The proportion of females rose with age. The proportion of current smokers fell, while that of non-smokers rose, with age ($p<0.001$). Age correlated negatively with total cholesterol and positively with high density lipoprotein cholesterol ($p<0.001$). There was no correlation between age and size or site of infarction. Complications, however, rose with age as did mortality, from 3% in the under-60s to 20% in those over 70 ($p<0.001$). Cardiogenic shock and left ventricular failure became significantly more lethal with rising age but ventricular fibrillation did not have a poorer outcome in older patients.

Coronary risk factors in the elderly differ significantly from those found in younger patients. Complications and mortality increase in the elderly following a first myocardial infarction, but ventricular fibrillation is treatable in these patients who should, therefore, still be admitted to the CCU. As the coronary population ages, however, management and secondary prevention methods derived from studies confined to younger subjects may become inappropriate.

Arrhythmia and prognosis in dilated cardiomyopathy

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The aim of this retrospective study was to assess the association between arrhythmia and prognosis in dilated cardiomyopathy (DCM). Follow up information has been obtained for 114 of 118 UK residents with DCM seen at this hospital since 1978. (74 men, 40 women, mean age 45). New York Heart Association (NYHA) class at diagnosis was class I in four; II in 90; III in 23, and IV in one patient. Ninety eight patients (86%) had 24 hour ECG monitoring 30(33) months after diagnosis; mean(SD). Arrhythmia was frequent; AF in 16, SVT in 24, VT in 36, couplets in 58, and >250 ventricular extrasystoles/24 hours in 57 patients. Twenty three patients (20%) have since died with disabling heart failure 48(40) months from diagnosis. Ten patients (9%) died suddenly when heart failure was not disabling (NYHA class I, II, III). Five patients have received cardiac transplants. Four patients died from other causes. Fifty eight of the 72 patients alive on medical treatment have remained stable or improved 77(54) months after diagnosis. Of the patients who died, 78% had VT or >250 extrasystoles/24 hours compared to 67% of patients still alive (NS). Thirty two patients received amiodarone (median dose 200 mg/day) for AF/SVT in 14, symptomatic VT in five, or asymptomatic ventricular ectopy in 13. After a mean of 41(28) months on treatment there have been no sudden deaths. Three patients stopped amiodarone because of side effects (thyrotoxicosis, n = two, pulmonary fibrosis, n = one). There have been 10 sudden deaths in 82 patients who have not received amiodarone a mean of 57 months from assessment.

In conclusion, arrhythmia was unhelpful in predicting sudden death in DCM and a possible role for amiodarone in its prevention needs prospective evaluation.

Mechanism of atrial natriuretic peptide release during tachycardia

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Atrial natriuretic peptide (ANP) concentrations are increased during paroxysmal tachycardia (PT) and also in conditions with increased atrial pressure. To see whether ANP release during PT is due to increased atrial rate or increased atrial pressure, we compared the ANP concentrations at different atrial pressures during identical tachycardia rates. We reduced atrial pressure during tachycardia by reducing venous return with balloon occlusion of the inferior vena cava (IVC). We compared the ANP responses to rapid atrial pacing over 50 beats per minute (bpm) increments from 200 to 350 bpm with and without IVC occlusion in six chloralose anaesthetised dogs. During incremental pacing without IVC occlusion there was a marked rise in pulmonary wedge pressure (PWP)—mean (SEM)—from 5·3(1·6) mm Hg at 200 bpm to 20·2(2·3) mm Hg at 350 bpm ($p < 0\cdot01$). At the same time, arterial and coronary sinus ANP concentrations rose from 116(55) and 339(91) to 1126(226) and 1960(456) pmol/l, respectively ($p < 0\cdot01$). In contrast, incremental pacing with IVC occlusion produced an insignificant increase in PWP from $-1\cdot0$(1·9) at 200 bpm to 2·3(1·8) mm Hg at 350 bpm. Arterial and coronary sinus ANP concentrations during IVC occlusion were respectively 208(126) and 388(159) at 200 bpm and 261(83) and 345(80) pmol/l at 350 bpm (NS). A similar pattern was observed at intermediate pacing rates, with IVC occlusion preventing not only the rise in PWP but also the increase in plasma ANP concentrations with increasing heart rate.

The release of ANP during tachycardia is primarily dependent upon increased atrial pressure and not atrial rate.

Diagnostic value of intravenous adenosine in patients with arrhythmias

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Establishing the correct diagnosis of arrhythmia has important therapeutic and prognostic implications, but is often difficult from the surface electrocardiogram. Clarification of the association between atrial and ventricular activity would aid diagnosis. Intravenous adenosine (dose range 2·5 to 20 mg, mean 7 mg) was given to 12 patients, seven men and five women aged 17–72 years (mean 52). All had paroxysmal tachycardias (rate 120–240 beats/minute, mean 174 bpm) with an apparently constant association between atrial and ventricular activity on their electrocardiograms. Adenosine clarified the diagnosis in all cases by its transient effect on atrioventricular (AV) nodal conduction. Supraventricular tachycardia with a re-entry mechanism involving the AV node was diagnosed in four patients in whom adenosine terminated the tachycardia by blocking AV conduction. In those patients with recurrent tachycardias, adenosine restored sinus rhythm in 14 of 15 episodes. Atrial tachycardia with 1:1 AV conduction was shown to be the diagnosis in two patients, and atrial flutter with 2:1 block in five. Adenosine produced a transient increase in AV block, slowing the ventricular response and revealing the atrial tachycardia. Ventricular tachycardia with 1:1 retrograde ventriculoatrial (VA) conduction was diagnosed in one patient in whom adenosine produced transient VA dissociation, with fusion and capture beats. Minor side effects, including flushing, chest discomfort, dyspnoea, and headache were common (83%) but of short duration. No adverse haemodynamic response occurred.

Adenosine has diagnostic, in addition to therapeutic, value in patients with arrhythmias.

Doppler diagnosis of broad complex tachycardias

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The differential diagnosis of broad complex tachycardia (QRS > 120 ms) remains an important clinical problem. This study describes the use of ascending aorta Doppler velocimetry to quantify stroke volume to assess whether its variability may be used as a marker of independent atrial activity and thus identify ventricular tachycardia (VT).

Twenty patients with regular broad complex tachycardia were studied, 11 with VT and nine with supraventricular tachycardia (SVT). The diagnosis and AV relation were established by electrophysiology. Ascending aorta Doppler from the suprasternal notch was recorded using the Quinton Exerdop, a stand alone continuous wave Doppler. The maximum acceleration, peak velocity, and stroke distance were derived from 20 consecutive beats. There was no significant difference between the stroke distance, acceleration, or peak velocity for VT and SVT. The coefficient of variation was then calculated to assess if their variability could distinguish VT and SVT. Stroke distance was found to be the most discriminating, with a 20% coefficient of variation being 91% sensitive, and 100% specific, for ventricular tachycardia and 100% sensitive, and 100% specific, for AV dissociation. The patient with VT and 1:1 retrograde conduction could not be distinguished from SVT. A coefficient of variation of 12% for peak velocity was 82% sensitive, 100% specific for VT, and 90% sensitive, 100% specific, for AV dissociation. A coefficient of variation of 25% for acceleration was 91% sensitive, 89% specific for VT and 100% sensitive, 90% specific, for AV dissociation.

This study shows that with Doppler imaging the variability of ascending aorta blood flow may be used to diagnose AV dissociation and VT in broad complex tachycardia. The simplicity of the technique should allow its use in the emergency setting.

Electrophysiological and antiarrhythmic effects of the acute class III actions of d-sotalol

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The importance of acute class III effects in arrhythmia management is controversial. The clinical value and electrophysiological effects of d-sotalol were investigated in 10 patients (nine men; mean age 48 years) with life threatening ventricular arrhythmias (mean episodes 4·5 (range 3–10) and drug failures 2·8). Flecainide had failed in six and amiodarone in three. After baseline electrophysiology, 1–1·5 mg/kg of d-sotalol was infused over 10 minutes. Repeat electrophysiological study 20 minutes later showed significant changes in RR interval (786 (157) to 916 (175) ms; $p < 0·05$), QT interval (368 (31) to 414 (46) ms; $p < 0·001$), right atrial effective refractory period (229 (46) to 271 (38) ms; $p < 0·025$) and right ventricular effective refractory period (229 (22) to 267 (35) ms; $p < 0·001$). Right ventricular monophasic action potentials, measured in five of the 10 patients, increased from 310 (55) to 335 (61) ms ($p = 0·02$). Ventricular arrhythmias were induced in all 10 patients before d-sotalol infusion and in eight afterwards (cycle length before was 257 (51) and after 273 (70) ms; p = NS). Ventricular arrhythmias did not recur on oral treatment in the two patients who were suppressed acutely. No arrhythmogenic effects were seen.

Despite clear evidence of acute class III effects, d-sotalol at this dosage had only modest success (20%) in controlling life threatening ventricular arrhythmias.

Accurate non-invasive prediction of arrhythmic events after acute myocardial infarction

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Accurate prediction of arrhythmic events (sudden cardiac death and sustained ventricular tachycardia) after myocardial infarction is desirable both to reassure those at low risk and to test effectively the value of antiarrhythmic treatment in those at high risk. A prospective study was carried out in 134 consecutive patients admitted with acute myocardial infarction using high gain, signal averaged electrocardiography (SAECG) and 24 hour ambulatory electrocardiography (tape) within one week of infarction. Ten patients were not suitable for SAECG (bundle branch block in seven, atrial fibrillation in two, and complete heart block in one), and a tape result was not available in 22 (two refused, in 20 there were technical or administrative problems). The SAECG was abnormal in 33 of 124 (27%); an ectopic frequency of >5/hour was present in 26 of 112 (23%). There was both an abnormal SAECG and >5 extrasystoles per hour in nine of 107 (8%). During two to 12 months follow up, 13 patients (10%) suffered an arrhythmic event (documented sustained ventricular tachycardia (VT) in five, suspected VT in one, and sudden cardiac death without apparent reinfarction in seven). Discriminant analysis showed the tests to have the following ability in the prediction of arrhythmic events—SAECG: sensitivity 85%, specificity 82%, predictive accuracy 33%; tape: sensitivity 88%, specificity 82%, predictive accuracy 27%; SAECG and tape: sensitivity 85%, specificity 98%, predictive accuracy 78%.

Though each of these tests used alone lacks specificity, the combination of the two appears to be accurate enough to be of clinical value in assessing arrhythmic propensity in patients after myocardial infarction.

Evolving indications for cardiac transplantation

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Between April 1981 and January 1987 100 cardiac transplants were performed in 96 patients (70 men, 26 women). Sixty seven patients were less than 50 years old, and 29 ranged in age from 50 to 64 years. Recipient diagnosis was similar in both age groups—cardiomyopathy 56%, coronary artery disease 34%, valvar 6%, and graft failure 4%. The one year survival has improved from 70% for the first 50 to 81% for the second 50. The majority of deaths (20) occurred within 90 days of surgery. Only one death was due to infection and there were only four graft losses (one successful retransplantation) due to rejection. Although one year survival of 86% is higher for patients over 50 years old compared with 69% for patients less than 50, the former group comprises most of the last 50. Functional status and cardiac function has improved from New York Heart Association class IV and left ventricular ejection fraction mean 15%, to class I and class II and ejection fraction mean 60%. Forty patients have had one or more coronary angiograms performed one to five years after transplantation. No patient has shown any segmental lesion(s) on follow up for 12 to 72 months (mean 28 months). All patients received aspirin treatment. The improved results are reflected in broadening donor and recipient criteria; we accept donor dopamine support of up to 15 μg/kg/min and a flight time of up to three hours.

The presence of pulmonary embolism, diabetes, treated infection, and the presence of peripheral or cerebral vascular disease are not contraindications to transplantation.

Coronary occlusive disease in the transplanted heart

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Accelerated coronary occlusive disease in the donor heart is an important determinant of survival after cardiac transplantation. Although the aetiology remains obscure, the initiating injury to the endothelium is probably immunologically induced. This presents early as diffuse narrowing of the small and medium sized vessels whereas later individual risk factors may contribute to progression of segmental disease affecting mainly the larger vessels. Between January 1979 and June 1985, 117 patients received orthotopic heart transplants. Initially all patients had coronary angiograms annually. More recently, the first angiogram has been carried out at two years. If normal, the next examination is at four years; if abnormal, at three years. Thereafter annual angiograms are performed. Eighty two of the 117 patients survived two or more years after transplantation (70%) and 208 angiograms have been performed between one and seven years after their transplant.

Angiograms have been graded according to a scale 0 = apparently normal; I = slight irregularity; II = definite change but less than 50% narrowing in one or more vessels; III = severe changes of more than 50% narrowing in diameter. Angiographic disease was evident in 18% and 25% of patients at two and five years, respectively.

There was wide variation in the time of onset, severity, and rate of progression. Three patients have had further transplants and nine have died, of whom three had necropsy evidence of occlusive disease within a year of an apparently normal angiogram. In addition, four patients, who died from rejection between six and 12 months after transplantation, showed marked narrowing of their coronary vessels due to diffuse myointimal proliferation.

Isometric exercise in the denervated human heart: a Doppler echocardiographic study

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The haemodynamic response of the denervated heart to isometric exercise has not to our knowledge been previously reported. Eight orthotopic heart transplant recipients (age 40 (10) years) and eight healthy controls (age 25 (7) years), age and sex matched to the donor hearts, were studied. Using a hand grip dynamometer each subject performed sustained exercise at 30% of maximal voluntary contraction for a period of three minutes. Cardiac output was measured using combined Doppler and cross sectional echocardiography before exercise, at 30 second intervals during exercise, and after exercise. Aortic velocities were recorded using continuous wave Doppler from the suprasternal notch. Simultaneous cross sectional echocardiographs of the aortic orifice and left ventricular M mode echocardiographs were recorded. In the control group cardiac output increased from 6·1 l/minute at rest to 8·1 l/minute after three minutes exercise ($p < 0\cdot001$), due to an increase in heart rate from 70 to 92 beats/minute ($p < 0\cdot001$) with no change in stroke volume. There was no significant change in left ventricular end diastolic and end systolic dimensions or ejection fraction. In the transplant group cardiac output, heart rate, and stroke volume remained unchanged throughout the period of exercise. There was, however, a small decrease in ejection fraction. In both groups there was an increase in stroke volume immediately after exercise ($p < 0\cdot01$).

In contrast to dynamic exercise, the denervated human heart is unable to increase cardiac output during isometric exercise, and Doppler echocardiography is a useful technique for the non-invasive measurement of haemodynamic changes during isometric exercise.

Prevalence and significance of coronary artery disease after cardiac transplantation in patients receiving cyclosporin and azathioprine

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Coronary artery disease (CAD) is a potentially serious late complication of cardiac transplantation. Its prevalence, influence on exercise capacity, left ventricular function, and late mortality have been examined in this study. Three hundred and sixty two patients underwent orthotopic cardiac transplantation between September 1982 and July 1987 and received cyclosporin (CYA) and azathioprine (AZA). The cumulative probability of development of CAD is 7·2, 12·5, and 18·5% at one, two, and three years after operation, significantly different from a group of historical controls who had received prednisolone and AZA and who had a cumulative probability of development of CAD of 15, 33, and 96%, respectively. All patients with CAD are in New York Heart Association Class I or II. In a specific group of patients investigated three years after transplantation, the duration of treadmill exercise in patients with CAD was 9·9(0·84) minutes and with normal coronary arteries (NCA) 11·6 (0·49) minutes ($p < 0\cdot001$). Left ventricular ejection fraction, determined by radionuclide angiography at rest, was 65·0 (4·8) in CAD and 69·0 (1·7) in NCA ($p < 0\cdot05$), and on exercise 73·3 (4·8) and 74·1 (1·6) (NS), respectively. The late (> 1 year) mortality in patients with CAD was two of 22 (9·1%) in a follow-up of one to 37 (mean 10·9) months. These deaths, however, constitute 67% of the mortality of all patients during this period.

This study shows that the prevalence of coronary artery disease in patients receiving double or triple treatment including cyclosporin A is significantly lower than conventional immunosuppression and that this complication carries a guarded though not serious prognosis in the medium term.

Diurnal variation in ECG QRS voltage

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A decrease of $> 20\%$ in summated peak to peak QRS voltage in leads I, II, III, V1, and V6 in cardiac transplant recipients has been associated with rejection. Although ECG voltage measurements are known to vary from day to day the possibility of physiological diurnal variation in QRS voltage has not to our knowledge been investigated. QRS voltage, duration and frontal axis, QTc interval, and heart rate were studied during 24 hours in 16 normal subjects. ECGs were obtained at 7pm, 11pm, and 7am. Electrode site, subject position, and ECG recorder were constant. Summated QRS voltage was lower at 7am (mean (SD) 4·65 (0·88) mV) than at 7pm (5·37 (1·04), $p < 0{\cdot}001$), or at 11pm (5·34 (1·04), $p < 0{\cdot}001$). This QRS voltage decrease was $> 20\%$ in four of 16 subjects. Heart rate was higher at 7pm (74·9 (12·9) bpm) than at either 11pm (68·8 (11·6), $p < 0{\cdot}02$) or 7am (68·7 (10·5), $p < 0{\cdot}05$). Change in QRS voltage did not correlate with heart rate change. QTc was shorter at 7am (387·2 (22·4) ms) than at 7pm (398·6 (27·4), $p < 0{\cdot}05$). QRS duration and axis did not change.

There is therefore a substantial diurnal variation in QRS summated voltage in normal subjects. Similar diurnal voltage changes in patients would have implications for the diagnosis of cardiac rejection and for assessment of infarct size and left ventricular hypertrophy by voltage measurement.

Why do angiotensin converting enzyme inhibitors affect mortality in chronic heart failure? Effects on β adrenergic receptor function

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The mechanism of the beneficial effects of angiotensin converting enzyme (ACE) inhibitors, as shown by the reduction in mortality from chronic heart failure (CHF) in the CONSENSUS study, is unknown. In CHF it has been shown that down regulation of β adrenergic function occurs due to chronic sympathetic nervous system overstimulation and that ACE inhibitor treatment reduces raised circulating catecholamine concentrations. An indirect assessment of β adrenergic receptor function may be made, in man, by assessing circulating lymphocyte β adrenergic receptor responsiveness (LBRR) in vitro. In this study the effect of captopril on LBRR was examined prospectively in eight patients with CHF. (five-New York Heart Association class III; three-class IV; mean age 60·2 (6·4) years; mean ejection fraction by cross sectional echocardiography 22·3 (4·1)%. LBRR was determined by measuring increases in intracellular cyclic AMP in response to stimulation, in vitro, by incremental concentrations of isoprenaline (IP) (10^{-3} mmol/l–50 mmol/l). Results, expressed as stimulated increase in cyclic AMP over basal measurements, showed increased responsiveness after six weeks treatment with captopril, across the concentration range. The results were significantly different at the 10^{-3} mmol/l and 1 mmol/l IP concentrations (112 (5·2)% and 147 (10·2)% respectively, ($p < 0{\cdot}025$); 122 (13·9)% and 151 (7·7)%, respectively, ($p < 0{\cdot}05$); mean (SEM) before and after treatment, respectively).

Severe CHF results in the down regulation of the β adrenergic receptor population. These data suggest that treatment with captopril has improved β adrenergic receptor function and may in part explain the known clinical benefit of ACE inhibitors.

Balloon dilatation of calcific aortic stenosis

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The place of balloon dilatation (BD) in the management of calcific aortic stenosis remains controversial. We have performed BD in 27 elderly patients (mean age 77, range 65–86) in whom valve replacement was contraindicated. Five patients were in the New York Heart Association (NYHA) class II, 15 in class III, and seven in class IV. Tamponade occurred in one patient after perforation of the ventricle by a guidewire. There have been no other major complications and no clinically apparent embolic events. Mean peak to peak aortic valve gradient fell from 66 mm Hg (range 20–116) to 46 mm Hg (range 0–92) immediately after BD. Mean aortic valve area (calculated by the modified continuity equation from Doppler velocity measurements before and one to seven days after BD) showed a slight increase from 0·5 cm^2 (range 0·2–0·9) to 0·6 cm^2 (range 0·2–1·1). Seventeen patients (63%) reported an improvement in symptoms after BD. Of 19 survivors, four are in NYHA class I, nine in class II and six in class III.

Eight patients (all in class III or IV before BD) have died, three of non-cardiac disease. In stenotic valves without commissural fusion BD may achieve only a small or temporary increase in valve area by stretching non-calcified tissue in the valve ring or rendering the cusps more pliable.

In elderly patients with calcific aortic stenosis, BD can provide palliation of symptoms with a low incidence of complications. The mean increase in valve area, however, is small and it cannot be regarded as an alternative to valve replacement in surgical candidates.

Follow up of patients after balloon dilatation of the mitral valve

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Of 11 patients undergoing dilatation of the mitral valve by a 25 mm diameter balloon, nine have been restudied one to four months later: one patient had died from respiratory disease shortly after dilatation and in one patient the balloon catheters could not be made to cross the resistant interatrial septum. At follow up cardiac catheterisation of these nine patients the mitral valve gradient had been reduced from 10·7 to 6·6 mm Hg (−38%) and resting cardiac output had risen from 3·37 to 4·04 l/minute (+20%): the mitral valve area had increased from 0·60 cm^2 to 1·30 cm^2 (+46%). There was no correlation between haemodynamic improvement at rest and the extent of mitral valve calcification. Before balloon dilatation four of the 11 patients had been unable to leave hospital because of breathlessness; all had associated severe medical problems in addition to their mitral stenosis and were considered unsuitable for or at high risk of operation. One of these patients died, but three were symptomatically improved and able to be discharged from hospital. Four of the other six treated patients showed symptomatic improvement; the remaining two patients had a moderate degree of mitral stenosis and were either unsuitable for balloon dilatation or required the larger 30 mm diameter balloon. Improvement was also seen in the echocardiographic features of the mitral valve disease.

Balloon dilatation of the mitral valve is an important and cost effective procedure for high risk surgical candidates and a useful alternative to mitral valvotomy in all patients with mitral stenosis.

Balloon dilatation of the pulmonary valve in neonates: technical considerations and results

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Balloon dilatation of a severely stenosed pulmonary valve (PV) was attempted in seven neonates. In three, the diagnosis had been made prenatally. Various technical difficulties were encountered at the time of cardiac catheterisation. In all of them the right ventricular (RV) pressure was at systemic or suprasystemic height. The arterial duct was widely patent in five. In one of these five it was not possible to cross the PV and he was referred for a surgical valvotomy. In two patients, placing the guide wire in a safe position in the pulmonary artery was time consuming and difficult. In the remaining two it was not possible to enter the branch pulmonary arteries and balloon dilatation was safely performed with the balloon catheter over a guide wire anchored in the descending aorta through the duct. In these patients it was difficult to judge initial success because of the presence of the widely patent duct. In the two without an arterial duct the balloon dilatation was performed by a standard technique. In one neonate balloon dilatation was performed as a staged procedure. At age 6 hours only a 3 mm coronary angioplasty balloon could be manipulated across the pulmonary valve. Repeat BD three weeks later with an 8 mm balloon reduced the RV pressure from 85 mm Hg to 30 mm Hg. Follow up cardiac catheterisation has been performed in three infants. Balloon dilatation failed in two, the RV pressure being at systemic height. One of them had a dysplastic PV. In the other, failure may be due to inappropriate balloon size; repeat dilatation was precluded by inferior vena cava thrombosis. Both have been referred for a surgical valvotomy. A good result has been confirmed in the remaining two children.

We conclude that balloon dilatation of the pulmonary valve in neonates is technically difficult and may not produce uniformly good results.

Value of Doppler echocardiography in balloon dilatation of aortic stenosis

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To assess the role of echocardiography in the promising new treatment method of balloon dilatation of aortic stenosis we used cross sectional echocardiography, Doppler, and colour flow imaging before, during, and after anterograde balloon dilatation in five patients, 76 to 87 years of age (mean 82). During the procedure cross sectional echocardiography was used to guide transseptal catheterisation and to show appropriate balloon positioning across the stenotic valve. Aortic valve morphology, left ventricular fractional shortening, peak gradients (Doppler) and the presence of aortic incompetence were assessed immediately before, one day, and one month after balloon dilatation. Following balloon dilatation the peak to peak catheter gradients dropped from 74 (24) to 42 (22) mm Hg ($p < 0{\cdot}001$). Peak instantaneous gradients dropped from 87 (20) to 55 (21) mm Hg ($p < 0{\cdot}001$). There was slight increase in aortic cusp separation on echocardiography in 45 patients though the fractional shortening remained unchanged. The valve morphology on the initial study was not useful in predicting the patient's outcome. All patients had only mild aortic incompetence and none developed any detectable change on colour flow mapping following the procedure. A small degree of left atrial to right atrial shunt was seen immediately after the transseptal procedure; this was not, however, seen subsequently. Repeat Doppler studies after one month showed no change in three patients, a 10% return towards the initial gradient in one, and a 31% return in another patient, who subsequently died.

We conclude that modern Doppler echocardiography helps the performance of balloon dilatation and is an invaluable tool for the long term follow up.

Park blade septostomy: results and selection of patients

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The technique of atrial septostomy using a blade tipped catheter has been used in our department in the past five years when balloon atrial septostomy has failed to achieve good atrial mixing, or when the septum is considered too tough for ballooning. Between 1982 and 1987 twenty blade septostomies were performed on 19 patients. Their ages ranged from 23 days to 8·5 years (mean 429 days). Eight had discordant ventriculoarterial connections as the main abnormality, six of whom had previous balloon septostomy (group 1). Eleven had right or left atrioventricular valve atresia (group 2). In group 1 the atrial gradient dropped from 5·7 to 3·2 mm Hg, whereas in group 2 it fell from 6·3 to 2·5 mm Hg after blade septostomy (NS). The oxygen saturation in group 1 rose in five patients. Four patients in group 1, and five patients in group 2, showed clinical improvement after the procedure. There were no major complications.

Blade atrial septostomy is effective in patients with restrictive atrial communication especially in the older infant and young child and in the presence of atrioventricular valve atresia. Neonates with discordant ventriculoarterial connections who fail to improve with balloon septostomy, however, are unlikely to benefit from this technique especially when dynamic left ventricular outflow obstruction contributes more to the cyanosis than inadequate atrial mixing.

Percutaneous balloon dilatation for infant aortic valve stenosis

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Percutaneous balloon dilatation was attempted in 13 consecutive infants with critical aortic valve stenosis. Their ages ranged from 1 day to 11 months (median 4 weeks) and their weights from 1·5 to 8·9 kg. Ten patients were in heart failure. Three had already undergone surgical valvotomy. The balloons were 5–12 mm in diameter (at least 1–2 mm smaller than the aortic valve measured on an aortogram). In two patients the valve could not be crossed and both died during subsequent operations. Another two patients died during manipulation of the balloon catheter. No benefit was obtained in a further patient who also died later during operation. Balloon dilatation was successful in the remaining eight patients, reducing their aortic valve pressure gradients from 65 (25) to 23 (16) mm Hg; mean (95% confidence intervals). Two of these eight patients subsequently died from heart failure related to other cardiac lesions. The six survivors have done well. Two required femoral artery thrombectomy. None developed appreciable aortic regurgitation. At follow up the maximum ascending aortic Doppler velocities ranged from 1·9 to 4·0 m/s after two to 23 months but, despite this evidence of increasing valve gradient, there has been lasting clinical improvement. None of the five patients weighing less than 3 kg survived long term, whereas six of eight patients heavier than 3 kg are alive and well.

Although an improvement in the results of percutaneous balloon dilatation can be expected with increasing practical experience and improved balloon catheter design, relief of aortic valve stenosis in patients weighing less than 3 kg is likely to remain difficult whether performed surgically or by balloon catheter.

Results of the first 200 percutaneous transluminal coronary angioplasties in a regional cardiac unit

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Between December 1982 and December 1986, 200 percutaneous transluminal coronary angioplasties (PTCA) were performed by a single operator. Two hundred and seven vessels were dilated in 170 patients. The overall primary success rate was 73%. There was a learning curve with the success rate rising from 68% to 88% from the first 50 cases to the last 50 cases. Vessel occlusion occurred in 16 patients (8%) and was usually managed conservatively so that only five cases (2·5%) were sent for urgent coronary artery bypass grafting (CABG). The incidence of myocardial infarction (80%) was not reduced by urgent CABG. There were two deaths (1%) in the series, one at the time of emergency CABG, the other during PTCA for an elderly patient with multivessel disease and poor left ventricular function. The symptomatic restenosis rate was 22%. PTCA procedures have been carefully costed at £1390, comparing favourably with £3638 for CABG in this unit.

These results have given us confidence to attempt the more complicated cases with multivessel disease that have formed 42% of the last 50 cases of the series.

Effect of change in reference diameter on percentage diameter stenosis measurement during and after coronary angioplasty

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Conventional assessment of coronary angioplasty (PTCA) is often based on the changes in percentage diameter stenosis of the dilated lesion. This measurement is dependent on two variables, the reference diameter (diameter of nearest normal segment) and the minimal lumen diameter. We investigated the changes in these two variables in 342 patients with 398 lesions who underwent successful PTCA. Patients were reinvestigated after angioplasty at one of four predetermined follow up times: 30 days, 60 days, 90 days, or 120 days. Measurements were performed using a quantitative automated edge detection system (CAAS). Following the PTCA the mean reference diameter was 2·93 (0·55) mm and the minimal lumen diameter 2·08 (0·43) mm, with no differences among the four groups. ($p = 0.17$, and $p = 0.34$, respectively). At follow up in the 30 and 60 day groups there were small non-significant changes in both the reference diameter and the minimal lumen diameter. At 90 and 120 days, however, there were highly significant reductions ($p < 0.0001$) in both the reference diameters, −0·17 (0·41) mm and −0·26 (0·44) mm, respectively, and the minimal lumen diameters −0·37 (0·54) mm and −0·42 (0·52) mm, respectively. Restenosis following angioplasty takes place predominantly after the first 60 days after angioplasty with evidence of continuing deterioration up to 120 days. The reference diameter also deteriorates at 90 and 120 days.

The significant change in the reference diameter will lead to an underestimation of the change in a dilated lesion if assessment of the change is based on percentage diameter stenosis alone.

Incidence, importance, and determinants of aortic regurgitation after anatomical correction of transposition of the great arteries

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To determine the incidence and severity of aortic regurgitation (AR) after anatomical correction of transposition of the great arteries, the postoperative aortic root angiograms of 55 children were evaluated. Angiograms were performed from four to 56 (mean 15·6) months after operation. AR was present in 25 patients (45%). This was trivial or mild in 24 patients (96%) as defined by the presence of an aortic regurgitant jet without pronounced opacification of the left ventricle. In one patient there was grade 3 AR (the only patient with an aortic regurgitant murmur). AR was present in 16 of 26 patients (62%) that had undergone preliminary pulmonary artery banding as part of a two stage corrective operation: three of eight patients (37%) that had primary correction with closure of ventricular defect, and two of 17 patients (12%) that had primary correction as a neonate. Measurements of the aortic root diameter at the level of the aortic commissures were significantly ($p < 0.05$) higher than normal values. Commissural diameter expressed as % of normal value (1SD) was 146 (24)% after two stage correction; 133 (21)% after primary correction with closure of ventricular septal defect, and 119 (19)% after primary correction as a neonate, suggesting that an increased commissural diameter is an important determinant of AR. The method of coronary artery transfer and presence of aortic anastamotic narrowing (present in four patients (6%)) did not influence the incidence of AR.

Trivial AR is common after anatomical correction and may be related to an increased diameter of the aortic root at commissural level. There has been no clinical evidence of progression of the degree of AR during the medium term; its long term importance, however, remains undetermined.

Complete repair of common arterial trunk

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From July 1974 to March 1987, 15 infants with common arterial trunk (14 type 1, one type 2) underwent complete repair, five cases (33·3%) as emergencies, at the Wessex cardiac surgery centre. At operation, mean age was 12 weeks (range 5 days–10 months) and weight 4·1 kg (range 2·5–7·5 kg). Surface cooling and profound hypothermic circulatory arrest were used in all cases with a mean arrest time of 63 46 min (range 47–86 minutes). Aortic homografts were used as the conduit, mean size 16·3 mm (range 15–18 mm). Three patients died postoperatively (25%), two of whom were emergencies. There were no late deaths. Mean follow up is 5·9 years (range 3 months–13 years). Eight patients survived a cardiac arrest in the early postoperative period of whom one has permanent cerebral damage. One patient who had truncal valve regurgitation preoperatively required aortic valve replacement four years postoperatively and the conduit was replaced at the same time. All survivors are well and recent Doppler echocardiography shows a mild gradient across the conduit varying from 16–36 mm Hg except in one recent patient weighing 2·5 kg who has a conduit gradient of 80 mm Hg and will require reoperation.

Complete repair of common arterial trunk in early infancy continues to give good clinical and haemodynamic results more than 13 years after operation.

Pulmonary atresia with ventricular septal defect and multifocal pulmonary blood supply: results of a policy of surgical unifocalisation

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Single stage repair is not possible in patients with pulmonary atresia and ventricular septal defect, multifocal blood supply, and small central pulmonary arteries. Between 1979 and 1986 unifocalisation surgery, aimed at reducing sources of pulmonary blood supply by connecting major aortopulmonary collateral arteries (MAPCAs) to central pulmonary arteries without sacrificing segmental perfusion, was performed in 26 patients with 3·9 (1 1) MAPCAs per patient. The aims were to provide palliation and prepare the circulation for definitive repair. Age at first operation was 2 weeks—13 years, median 2 years, with eight being less than 1 year old. There were four deaths (15%). The number of bronchopulmonary segments connected to the central pulmonary artery increased from 5·5 (4·9) to 8·7 (5·4) ($p < 0.001$) and central pulmonary artery growth occurred (RPA + LPA/descending aorta ratio increased from 0 64 (0·61) to 0 95 (0·60), $p < 0.01$). This was accompanied by improvement in symptoms and systemic oxygen saturation. At restudy systemic artery to central pulmonary artery grafts had a better patency rate than did grafts or anastomoses involving MAPCAs (21 of 22 and 20 of 33, respectively, $p = 0.003$). Subsequent repair was performed in two (8%) patients with one death, and only four (15%) others are considered correctable.

Unifocalisation provided reasonable palliation at the cost of appreciable mortality. The increases in central pulmonary artery size and connection obtained in these complex young patients were modest and rarely permitted complete repair.

Waterston shunt revisited

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In recent times the modified Blalock-Taussig operation has become the systemic pulmonary shunt of choice in most centres and the Waterston anastomosis has fallen into disuse. In this unit, however, the Waterston shunt has continued to be the first shunt of choice particularly in small infants, and this paper presents our experience over a seven and a half year period from 1979–1986. Included are 74 consecutive infants ranging in age from 1 day to 20 months (median 5 weeks) whose weights ranged from 1·8–9 kg (median 3·6 kg). The major diagnostic categories were tetralogy of Fallot (31%), pulmonary atresia and ventricular septal defect (21%), pulmonary atresia and intact ventricular septum (17%), tricuspid atresia (5%), and the remainder comprised a heterogeneous group of complex lesions with reduced pulmonary blood flow. There were six operative deaths (mortality 8%), and four infants required reoperation for early shunt failure one day to three weeks postoperatively. The maximum follow up is 92 months (average 25 months) and there have been 11 late deaths, none related to shunt failure. Corrective surgery has been performed in eight children at a median period postoperatively of 46 months and seven further children are due to be corrected in the near future. Seven of the 68 children discharged from hospital have required a second shunt at a median of 31 months postoperatively.

We believe these results support the continuing use of the Waterston anastomosis, particularly in small infants.

Fate of children with tricuspid atresia presenting in infancy

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We reviewed the clinical outcome of 225 patients with tricuspid atresia who presented within the first year of life between 1972 and 1987. Ventriculoarterial connection was concordant (CONC) in 151 (67%), discordant (DISC) in 58 (26%), and neither in 16 (7%). There was evidence of systemic outflow obstruction at presentation in 34 (54%) of patients with DISC (subaortic stenosis in nine, coarctation in 13, both in 12). Cox regression identified systemic outflow obstruction, ECG left ventricular strain, and presentation at a younger age or without cyanosis as independent adverse risk factors for survival. The actuarial survival was similar for patients who underwent a systemic to pulmonary artery shunt and for those who had pulmonary artery banding alone (79% and 81% at one year, and 66% and 63% at five years, respectively). Only two of 25 (5%) patients with coarctation survived beyond one year of age, despite surgery in 17 of 25 (68%). As a result, patients with DISC had a five year actuarial survival significantly worse than patients with CONC (34% and 61%, respectively, $p = 0{\cdot}0001$). There were 82 patients with CONC and 18 patients with DISC who survived beyond two years of age. Of these patients, 70 of the 76 (92%) with CONC and 11 of the 15 (73%) with DISC who have been recatheterised, fulfilled the criteria for a definitive repair by a modified Fontan operation.

The majority of patients with tricuspid atresia and ventriculoarterial concordance will be suitable for eventual definitive surgery. Patients with ventriculoarterial discordance, however, often have systemic outflow obstruction at presentation resulting in a much poorer prognosis despite palliative intervention.

Incidence and site of pulmonary stenosis after anatomical correction of transposition of the great arteries

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Supravalvar pulmonary stenosis (PS) is a well recognised complication of anatomical correction of transposition of the great arteries. To investigate the incidence and site of obstruction, we performed right heart catheterisation and right ventriculography in 66 patients between 1·3 and 50 (mean 14) months postoperatively. Pulmonary artery reconstruction had been performed by direct anastamosis as described by Le Compte in 45 patients (68%) by direct anastamosis without Le Compte's manoeuvre in seven patients (11%); using a dura tube in 11 patients (17%), a Dacron tube to the right of the aorta in two patients (3%), and with a pericardial tube in one patient (2%). The right ventricular systolic pressure for the whole group ranged from 18 to 95 (mean 46) mm Hg. The right to left ventricular systolic pressure ratio (RV:LV) ranged from 0·2 to 1·5 (mean 0·5). Significant PS (defined as RV:LV $> 0{\cdot}5$) was present in 23 patients (35%) and was most common in those that had undergone primary correction during the neonatal period (nine of 22 patients (41%)) compared with those having a two stage operation (eight of 30 patients (27%)). The site of obstruction was the pulmonary anastomosis in 14 patients, branch pulmonary arteries in two, dysplastic pulmonary valve in three, and kinking of a Dacron tube in two. In two patients no obvious site of obstruction was identified. Apparent branch pulmonary artery narrowing was present in 59% of those corrected as neonates compared with 9% of the remaining patients. The mean pulmonary valve annulus diameter for all patients was 65% of normal values ($p < 0.05$). Three patients have undergone successful reoperation to relieve severe PS.

Supravalvar PS continues to be an important problem after anatomical correction and further investigation of its aetiology is required.

Can colour flow mapping improve the assessment of lung blood supply in pulmonary atresia with ventricular septal defect?

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The decision to perform an aortopulmonary shunt in a neonate with pulmonary atresia and ventricular septal defect must be based on accurate knowledge of lung blood supply. Angiography will normally identify adequately sized confluent pulmonary arteries and exclude multiple collateral vessels. Potentially ultrasound imaging with colour flow mapping (CFM) could provide information essential to surgical decision making. Ultrasound information derived from 27 infants has been compared with angiographic data. Imaging consistently predicted the absence of adequately sized central pulmonary arteries in eight patients, identifying the presence of two or more descending aortic collaterals in all such cases. CFM confirmed collateral flow patterns and accurately predicted proximal collateral stenosis. Where central pulmonary arteries were present (and collaterals absent) pulmonary artery continuity was correctly predicted in 14 of 16 patients using imaging alone. CFM confirmed pulmonary artery continuity in all 16. In three patients right and left pulmonary arteries were discontinuous. This was not diagnosed by imaging in any case, but was predicted in all three by CFM. In two additional cases a CFM flow disturbance correctly predicted appreciable central pulmonary artery stenosis.

Major problem areas were defined: (a) imaging did not differentiate dual duct supply from multiple collaterals; (b) imaging could not consistently identify lower thoracic collaterals or those from the head and arm vessels; and (c) the distal morphology of the pulmonary vessels was not defined. In every case, however, sufficient information was derived from imaging plus CFM to allow an accurate non-invasive assessment of the need for aortopulmonary shunting.

Myocardial fibrosis in tetralogy of Fallot: effect of surgery or part of the natural history?

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Arrhythmia and ventricular dysfunction are recognised complications after repair of tetralogy of Fallot and have been linked to sudden death. We have studied right and left ventricular myocardium in 28 patients with tetralogy of Fallot who died before or at repair (<1 year–11 patients, 1–5 years—12 patients, >5 years—five patients) to determine whether myocardial damage occurs as part of the natural history over and above the effects of surgery itself. Semi-automated analysis of fibrous tissue content was performed on sections from right ventricle and left ventricle inlet, apex and outflow tract (60 fields/block), and the results compared with 62 normal hearts. Fibrous tissue in the left ventricle remained normal in all age groups. In contrast, fibrous tissue in the right ventricle was normal in patients <1 year (2·1 g (0·96) in controls and 2·2 g (1·5) in tetralogy of Fallot) but there was an abnormal increase in fibrous tissue with age (19·8 g (9) in controls >5 years, and 43·3 (21) in tetralogy of Fallot >5 years, $p < 0.05$). This was maximal in the outflow tract and in the subendocardium.

Progressive damage to the right ventricle occurs with increasing age even before repair of tetralogy of Fallot. This may be the substrate for late postoperative complications and argues in favour of early repair.

Calcific aortic stenosis: a complication of chronic uraemia

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The incidence of aortic stenosis (AS) was investigated in a retrospective clinicopathological study of 174 patients with end stage renal disease

(ESRD). Six patients developed severe calcific AS a mean 9·7 years after starting haemodialysis (HD), which was significantly greater than the expected incidence ($p = 0{\cdot}004$). In five patients (mean age 50·8 years) AS was caused by severe premature calcification of a tricuspid aortic valve. The aetiology of premature aortic valve calcification (AVC) and stenosis was studied in a prospective echocardiographic study of 87 patients aged between 35 and 70 years on maintenance HD. Five patients had stenosis of a tricuspid aortic valve from premature AVC (mean age 52 years, mean duration of HD 9·4 years). Patients with AVC were older (55 and 50 years, respectively, $p < 0{\cdot}02$) and had received HD for longer (9·4 and 6·8 years, respectively, $p < 0{\cdot}05$), and had a higher calcium phosphate product ($p < 0{\cdot}001$) than those without AVC. There was a significant association between the presence of AVC and calcification of the mitral annulus ($p < 0{\cdot}05$).

Premature AVC is common in patients on long term HD and appears to be associated with abnormal calcium and phosphate metabolism and possibly increased stress on the valve cusps from hypertension and increased cardiac output. In a small but important group of patients severe AVC produces AS. Thus calcific AS can be considered as a complication of ESRD.

Increase in aortic valve gradients with time: a long term retrospective study

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In patients with valvar aortic stenosis the decision to undertake valve replacement is influenced by the catheter withdrawal gradient. It is unclear whether the gradient increases in patients whose initial gradient indicates that surgery is unnecessary. Records of patients with an aortic valve gradient, who had undergone previous catheterisation, were identified and their initial investigation was reviewed. Thirty four such patients were found; their mean age was 53 years (range 22 to 68). The mean initial gradient was 17 mm Hg (range 0 to 60 mm Hg) and the mean second gradient was 53 mm Hg (range 15 to 120). In all but two cases the gradient had increased, and the average rate of change was +8·0 mm Hg per year. Twenty three of the 34 subsequently underwent aortic valve replacement. In 10 of the patients no initial gradient had been found and in this group the mean gradient at reinvestigation was 44 mm Hg (range 25 to 65 mm Hg) after 7 years (range two to 10). In the 24 patients with an initial gradient, this changed from a mean of 24 mm Hg (range 10 to 66 mm Hg) to 56 mm Hg (range 15 to 120 mm Hg) after six years (range one to 17). The rate of progression was not significantly correlated with age, the initial gradient, the presence of calcification, or the diagnosis of rheumatic or non-rheumatic heart disease.

Aortic valve gradients which are not important may become so with time. Our results suggest that aortic valve replacement should be considered in patients with minor gradients in whom cardiac surgery is to be undertaken for other reasons.

Doppler echocardiography in aortic valve disease: limitations in the presence of aortic incompetence

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Aortic incompetence (AI) complicates accurate Doppler measurement of systolic aortic gradients. To assess the relation between the severity of AI and errors in the Doppler measurement of peak aortic gradient, we performed continuous wave Doppler one to three days before aortic angiography and haemodynamic measurement of peak to peak aortic valve gradient in 50 patients aged 65 years (range 10–86 years) with aortic valve disease. Doppler acceleration rate was calculated (m/sec^2) as the peak velocity (m/sec) normalised to acceleration time (sec) which is defined as the time from the onset to the peak of systolic aortic flow. The systolic aortic jet was located by colour coded flow mapping. AI was angiographically mild (grade 0–2/4) in 35 of 50 patients (70%) and moderate to severe in 15 of 50 patients (30%). Peak to peak catheter gradient was 54 (24) mm Hg (range 10–110) with Doppler calculated peak gradient 74 (25) mm Hg (range 29–118). The Doppler gradient overestimated the catheter gradient by 19 (14) mm Hg (range 1–60). Doppler acceleration rate was 40 (6) m/sec^2 (range 24–55). This was related to the difference in Doppler and catheter gradients ($r = 0{\cdot}55$, $p < 0{\cdot}001$) and independent of the severity of aortic stenosis $r = 0{\cdot}07$, (NS). In patients with severe AI the Doppler overestimation was greater (33 (16) and 14 (8) mm Hg, respectively) ($p = 0{\cdot}001$) and the Doppler acceleration rate was greater (47 (3) and 37 (5) m/sec^2, respectively) ($p < 0{\cdot}0001$). All patients with severe AI had acceleration rates of more than 45 m/sec^2.

Moderate to severe AI complicates accurate Doppler measurement of systolic aortic gradients. Doppler acceleration rate is a non-invasive index able to depict the contribution of AI to the generation of Doppler gradients.

Echocardiographic left ventricular wall dimensions to grade the severity of aortic stenosis: a historical myth

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Left ventricular hypertrophy as characterised echocardiographically is a useful indicator of the presence of aortic stenosis (AS) but is also used to grade the severity of obstruction. To test the validity of this we compared M mode echocardiographic measurements of the septum and posterior wall with Gorlin aortic valve area (GAVA) derived at cardiac catheterisation. Three hundred and thirty patients with good quality echocardiograms who underwent cardiac catheterisation for AS were studied. Patients with grade 3 or 4 aortic regurgitation or no significant aortic gradient were excluded. The GAVA was calculated from the mean aortic valve gradient, systolic ejection period, and dye dilution derived cardiac output. The correlation was then calculated between the GAVA and the left ventricular wall dimensions. The correlation coefficients were poor, $r = 0{\cdot}13$ for the septum and $r = 0{\cdot}15$ for the posterior wall. The maximum diagnostic accuracy for severe AS (defined as a GAVA $< 0{\cdot}70\ cm^2$) for the range of wall dimensions was 16% for a septum $> 1{\cdot}2$ cm and 15% for a posterior wall $> 1{\cdot}2$ cm. The correlation with other haemodynamic variables was better, peak left ventricular systolic pressure having r values of 0 37 and 0 30 for posterior wall and septum, respectively. Mean and peak aortic valve gradient had r values approaching 0·30 for both dimensions. The correlation coefficient with systolic arterial pressure and cardiac index approached zero.

These data demonstrate that the left ventricular wall dimensions correlate poorly with GAVA and should not be used to grade AS. As the wall dimensions correlate better with the aortic valve gradients than the valve area they will tend to compound any error in grading aortic stenosis when the area is not calculated.

Tolerance to nitrates: does it occur and how long a nitrate free period is required to prevent it?

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We have investigated whether the loss of therapeutic effect of transdermal nitrate preparations is due to tolerance (rather than system failure), how rapidly this tolerance develops, and how long a nitrate free period is required to prevent it.

A randomised, double blind, crossover trial studied exercise tolerance during treatment with 10 mg glyceryl trinitrate patches for two consecutive days on four successive weeks in 12 patients with angina (mean age 57·5 years). Three active or dummy patches were applied continuously for 32 or 36 hours. Exercise testing was performed at 1200 and 1700 or 2100 hours on each day. The timing and order of active and dummy patches varied with each treatment period so that the effect of continuous treatment was tested at 3, 8, 12, 15, and 24 hours, and intermittent treatment on two consecutive days using two different nitrate free periods (12 hours or 16 hours). The results showed a significant treatment effect at three and eight hours, a reduced effect at 12 and 15 hours which was no longer significant and by 24 hours there was no effect at all Thus during continuous treatment tests on day two were significantly worse than on day one and no better than placebo. Both nitrate free periods prevented the development of tolerance such that tests on day two remained significantly better than placebo. Although exercise measurements on day two were slightly worse than on day one during intermittent treatment this was not significant overall.

This study confirms that loss of effect from transdermal nitrates is due to tolerance, that its onset is between 8–12 hours but is not complete until after 15 hours. It is prevented by nitrate free periods, and 12 hours may be sufficient although there was a suggestion that this was less effective than 16 hours.

Efficacy of captopril and enoximone in stable severe heart failure

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The relative efficacy of captopril 25 mg three times a day (C), an established ACE inhibitor, and enoximone, a new inotrope, 100 mg three times a day (E), was tested in 12 patients with stable New York Heart Association (NYHA) classes III–IV heart failure. A randomised, double blind, crossover protocol was adopted and haemodynamic data recorded at rest and exercise before randomisation and at the end of each six week treatment phase. Cardiac power output derived from pre load arterial pressure and cardiac output was used as a measure of cardiac performance. Although NYHA class improved on both drugs from a mean (SE) of 3·4 (0·1) to 2·7 (0·2) (C) and 2 5 (0·2) (E), $p < 0·02$, grouped data failed to show improvement in exercise time, or rest or exercise haemodynamics. Exercise time, however, improved by $>20\%$ in six patients; five on enoximone and one on captopril. At baseline these responders (R) to treatment had a greater capacity to increase cardiac output with exercise (ΔCPO = 0·88 watts (R)) compared to non-responders (NR) (0 55 watts). All five who responded to the inotrope did so following six weeks of captopril treatment and their increase in exercise capacity was matched by an enhanced exercise related increase in CPO (ΔCPO = 1·15 (R) vs. 0·64 (NR) watts).

These results suggest that enoximone may benefit some patients by increasing their functional cardiac reserve. The responders received captopril before the inotrope suggesting that prior ACE inhibition may enable the heart to respond to inotropic stimulation, perhaps mediated through up regulation of the β receptor.

Isoprenaline, dopamine, and dobutamine infusions all cause hypokalaemia

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Swings in potassium accompany infusions of adrenaline and isoprenaline but the commonly used inotropes, dopamine and dobutamine, were thought not to cause hypokalaemia. We have tested the effect of these drugs on short term potassium homeostasis in a controlled manner in dogs. Isoprenaline (0·1 μg/kg/minute), dopamine, and dobutamine (both 15 μg/kg/minute) were given by infusion over 30 minutes while arterial potassium changes were followed continuously with a catheter tip potassium selective electrode. Infusions were preceded and followed by 30 minute control periods of 0·9% saline infusion. Eight infusions of each drug were given to six adult beagles. As with other catecholamines, there was a consistent, transient, but small rise (0·1 mM) in potassium concentration with all three drugs followed by a more profound hypokalaemia which was sustained for the duration of the infusion The mean (1 SD) fall in potassium concentration was 0·80 (0·19) mM for isoprenaline, 0·71 (0 26) mM for dopamine, and 0·68 (0·29) mM for dobutamine, and over 1·0 mM in some instances with all three drugs. Ventricular ectopy developed in two dogs during dopamine infusion and resolved during the control (saline) infusion when the potassium concentration was returning towards normal.

The potential implications of these findings on clinical practice have encouraged us to investigate the possibility that similar changes occur in man.

Effect of low maintenance dose Ω 3 fatty acids on serum lipid concentrations

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A fish oil concentrate rich in eicosapentaenoic and docosahexaenoic acids has been shown to reduce serum cholesterol and triglycerides and raise high density lipoprotein concentrations. These studies have entailed ingestion of large quantities of fish oil which has proved unacceptable to many patients. This pilot study was designed to assess the effects of lower doses of fish oil. We studied 21 patients who had raised cholesterol and triglyceride concentrations despite adherence to an individualised restricted diet. The patients were divided into two comparable groups, A and B, and the study was performed in a modified double blind crossover fashion. Group A (10 patients) received a loading dose of 3000 mg (10 capsules) of fish oil daily (a combination of 180 mg of eicosapentaenoic acid and 120 mg of docosahexaenoic acid per capsule) for one week, followed by 900 mg (three capsules) daily for 12 weeks. They then received three placebo capsules daily for a further 12 week period. Group B (11 patients) received 10 placebo capsules daily for a week, followed by three placebo capsules daily for 12 weeks, continuing to 900 mg fish oil (three capsules) daily for 12 weeks. Results showed a significant reduction in serum triglyceride concentrations in group A over the initial loading week ($p < 0·05$). This reduction was maintained by the lower dose over the following 12 weeks ($p < 0·01$ over the 13 week period). There was no significant change in serum triglyceride concentrations in group B (no loading period) or in the placebo treated group. There was a significant rise in high density lipoprotein concentrations in group A over the loading week only ($p < 0·02$) but this rise was not maintained over the following 12 weeks (p = NS over the 12 week period). No change in high density lipoprotein concentrations in group B were observed. No significant changes in serum cholesterol or low density lipoproteins were noted in either group.

These results suggest that short term high dose fish oil with lower maintenance doses is effective in reducing hypertriglyceridaemia. No effect on total cholesterol was seen. It would appear that high maintenance doses of fish oil are required to sustain a rise in high density lipoprotein concentrations.

Calcium exchange in rabbit myocardium during and after hypoxia: role of sodium calcium exchange

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The association between calcium uptake on reperfusion or reoxygenation of myocardium and the recovery of contraction is disputed and the cause unknown. Sodium calcium exchange is a potential mechanism. Calcium uptake was measured using $^{47}Ca^{2+}$ in the isolated and arterially perfused interventricular septum of the rabbit. Temperature was 35°C and the stimulation rate was 90 beats/minute. No change in tissue uptake of calcium occurred during substrate free hypoxia ($n = 7$) for 45 minutes but on reoxygenation tissue calcium uptake increased by 73 (7)%. Recovery of mechanical function was inversely related to the increase in tissue calcium. Stimulation of sodium calcium exchange by perfusion with a sucrose solution low in sodium, and without potassium, ($n = 10$) increased tissue calcium by between 18 and 136% and the relation to mechanical recovery was similar to that observed on reoxygenation after a period of hypoxia. Sodium calcium exchange could be stimulated during hypoxia ($n = 6$). Lithium (100 mmol/l/second) substitution for extracellular sodium inhibited sodium calcium exchange under control conditions ($n = 3$). Substituting lithium (100 mmol/l/second) for sodium (100 mmol/l/second) during the last 35 minutes ($n = 6$) and the last 10 minutes ($n = 8$) of the 45 minute period of hypoxia and the first 20 minutes of reoxygenation resulted in an increase in $^{47}Ca^{2+}$ uptake of 69 (9)% and 79 (9)%, respectively, similar to when lithium was not used. Recovery of mechanical function was not affected by lithium. Inhibition of sodium hydrogen exchange during hypoxia and reoxygenation by amiloride (10^{-4} mmol/l/second) had no effect on the reoxygenation induced uptake of calcium.

The increase in calcium uptake that occurs on reoxygenation after a period of substrate free hypoxia in this experimental model is related to the recovery of mechanical function, but sodium calcium exchange is not a major mechanism.

Accelerated intraventricular systolic flow differentiates patients with hypertrophic cardiomyopathy from those with secondary causes of hypertrophy

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The diagnosis of hypertrophic cardiomyopathy (HCM) is based on being able to show unexplained left ventricular hypertrophy (LVH). Echocardiography is the best technique for detecting LVH but it is not specific for the diagnosis of HCM as opposed to other causes of hypertrophy. To determine whether the intraventricular flow profile is specific in HCM we performed intraventricular flow mapping in 27 patients with HCM (14 with and 13 without left ventricular (LV) gradient), 25 patients with secondary LVH (10-aortic stenosis, 10-systemic hypertension, five-cardiac amyloidosis) and 10 patients with mitral regurgitation. Ten normal subjects were studied for comparison. A Toshiba SSH 65 A was used at a fixed PRF (4 KHz) with a 2·5 MHz transducer. The presence and position of intraventricular aliasing or turbulent (mosaic) flow on colour Doppler was noted. Then sequential peak velocities (cm/second) were obtained with unigate pulse Doppler at the apex, papillary muscles, LV outflow tract, and ascending aorta. Patients with HCM (apex 36 (5), papillary muscle 78 (16), LV outflow 212 (154), aorta 104 (13) had significantly higher intraventricular flows when compared with aortic stenosis (26 (4), 41 (5), 67 (4), and 390 (42), $p < 0{\cdot}001$), hypertensives (28 (3), 48 (6), 72 (7), and 95 (6), $p < 0{\cdot}001$), cardiac amyloid (22 (2), 34 (3), 63 (3), and 72 (5), $p < 0{\cdot}00001$), mitral regurgitation (29 (4), 54 (15), 75 (4), and 96 (6), $p < 0{\cdot}001$) and the normal individuals (23 (2), 41 (5), 67 (9), and 96 (1), $p < 0{\cdot}001$). There was no overlap of peak intracavitary flow velocities in HCM when compared with secondary LVH. Thirteen patients, however, with HCM and no gradient fell within the ranges detected in mitral regurgitation.

Patients with HCM have increased velocities with progressive acceleration of intraventricular flow which distinguish them from secondary LVH.

Magnetic resonance imaging of infants with congenital heart defects

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We have studied 12 infants with various congenital heart defects (aged 4 days to 3 months) by cardiac magnetic resonance imaging (MRI). A 1·5 Tesla whole body imaging system and a 32 cm diameter head coil were used. Eight were studied without sedation. Five millimetre electrocardiogram gated sections were acquired using a spin echo sequence. A matrix size of 256 × 256 was used. Oblique imaging was used to provide optimal imaging of cardiac malformations. Typical scan time for a series of seven sections was six minutes. The images were of good quality in all cases. MRI was found to be of special value in studying seven patients with suspected abnormalities of the aortic arch. The anatomy of proximal pulmonary arteries was well shown including a Blalock Taussig shunt in one patient. Absence of central pulmonary arteries and the presence of collateral arteries was shown in a further case. In two patients with ventricular septal defects the anatomy was well defined, in one case showing multiple trabecular defects which had not been evident on angiography. Systemic and pulmonary venous connections were well shown, including one case of anomalous pulmonary venous connection. The morphology of atrial and ventricular chambers was clearly delineated. The demonstration of the arterial connections was excellent in a case of double outlet of the right ventricle. Resolution was not adequate to identify an anomalous coronary artery in one case.

Superior resolution with high field strength MRI systems make them especially suitable for the investigation of heart defects in this age group.

Atrial natriuretic peptide in spontaneous tachycardia

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Venous atrial natriuretic peptide concentrations (ANP) were measured by radioimmunoassay during and following conversion of spontaneous tachycardias, to determine the effect of tachycardia on ANP. We studied 34 consecutive patients, aged 29–84 years, with spontaneous tachycardias of 0·5 hours to 100 days duration. Sinus rhythm was restored by direct current cardioversion under thiopentone anaesthesia ($n = 18$), pharmacologically ($n = 13$), or spontaneously ($n = 3$). ANP during tachycardia ranged from 17–525, mean (SEM) (140 (23) pmol/l, and was highest in ventricular tachycardia (332 (58) pmol/l, $n = 7$), and concentrations in supraventricular tachycardia (120 (39) pmol/l, $n = 5$) and atrial fibrillation (85 (11) pmol/l, $n = 22$) were higher than normal (range 8–24 pmol/l). ANP was higher in patients with structural cardiac disease than in those without (170 (28) and 59 (21) pmol/l, respectively, $p < 0·05$). ANP and systolic arterial pressure during tachycardia correlated negatively ($r = -0·60$, $p < 0·001$); ANP, however, was only weakly related to the ventricular rate ($r = 0·31$, NS) and the duration of the tachycardia ($r = -0·18$, NS). After conversion of the tachycardia to sinus rhythm ANP fell to 116 (17) pmol/l at five minutes and 101 (19) pmol/l at 15 minutes ($p < 0·01$ and $p < 0·02$, respectively, compared with ANP during tachycardia).

We conclude that ANP is raised during tachycardia with the highest concentrations being observed during ventricular tachycardia and in patients with structural cardiac disease. The ANP concentrations observed during tachycardia are within a range known to have biological effects in man.

Are changes in plasma catecholamine concentrations responsible for the failure of acute phase β blockade to limit infarct size?

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Despite a 15% reduction in mortality, neither the MIAMI nor ISIS-1 trials reported a significant reduction in enzymatically estimated infarct size in patients receiving β blockers. Therefore 20 patients with acute myocardial infarction were randomised blindly to treatment with intravenous, followed by oral, metoprolol or placebo. Patients were haemodynamically monitored for 24 hours. Plasma adrenaline (AD) and noradrenaline (NAD) concentrations were estimated at baseline (mean 6·0 (0·9) hours from onset of symptoms), and one and 24 hours from start of treatment. Plasma AD and NAD were raised in all but one patient, with a further increase in those receiving metoprolol ($p < 0·05$). At baseline pulmonary wedge pressure was directly related to both AD ($r - 0·44$; $p < 0\ 05$) and NAD concentrations ($r - 0·44$; $p < 0·05$) while stroke volume index was inversely related to NAD ($r - 0·44$; $p < 0·05$). From baseline to one hour the change in systemic vascular resistance was related to the increase in both AD ($r - 0\cdot48$; $p < 0\cdot05$) and NAD concentrations ($r - 0\cdot66$; $p < 0\cdot01$).

In acute myocardial infarction high plasma catecholamine concentrations were associated with the haemodynamic markers of severe left ventricular damage. β blockade produced a further rise in catecholamine concentrations which was associated with a rise in systemic vascular resistance. The resulting increase in myocardial oxygen consumption may, in part, explain the limited impact of β blockade on myocardial salvage in acute infarction.

Myocardial dysfunction in ankylosing spondylitis

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Echocardiographic evidence has suggested there are abnormalities of myocardial function in patients with ankylosing spondylitis (AS). We have further evaluated cardiac function in patients with AS and in normal volunteers (NV). We studied 24 NVs and 21 patients with AS in the age range 18–45. None had overt cardiac disease. Cardiac function was assessed at rest and during supine bicycle exercise using radionuclide angiography in the LAO position following equilibration with 740 MBq of technetium-99. Subjects undertook supine bicycle exercise with 30 watt increments every three minutes to the point of fatigue. Comparisons of NV and AS patients' data were made using the Student's *t* test for independent samples or the Mann-Whitney nonparametric test, as appropriate. Subjects were matched for age, sex, height, and weight. Global left ventricular function showed several differences between NV and AS. Peak filling rate during exercise was significantly lower in AS (NV 6·5, (SD 1·2); AS 5·7 (1·2), $p = 0\cdot026$). Time to reach peak filling during exercise was significantly lower on exercise in AS (NV 102, (22), AS 120 (23), $p = 0\cdot012$). Wall motion was abnormal at rest and on exercise in AS $p = 0\cdot00004$. Regional analysis also showed differences between AS and NVs both at rest and on exercise. In the anteroseptal region, filling fraction and peak filling rate were significantly lower in AS $p = 0\cdot044$. Most of the differences were in variables of diastolic function.

This study shows that there are abnormalities in cardiac function in AS. The major abnormalities are in diastolic function suggesting a decrease in LV compliance.

Hypercoagulability, consumptive coagulopathy, and paradoxical reduction of platelet aggregation in infective endocarditis

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Local and generalised changes in coagulation may be important in the genesis of vegetations and embolism in infective endocarditis (IE). To characterise such alterations, serial haematological investigations were performed on consecutive cases of IE. Preliminary data are presented here as clear patterns of abnormality emerged quickly. Platelet survival was measured by indium-111 labelling. Acute and convalescent samples were analysed for fibrinogen, factor VIII, antithrombin III (AT3) and fibrin degradation products (FDPs) by standard methods, as well as adenosine diphosphate and collagen induced platelet aggregation. Five patients had a high fibrinogen concentration (5·0–10·6, mean 8·02 g/dl normal range, n̄, 2–4) and a high normal factor VIII concentration (120–180%, mean 144% n̄ 50–200%) with a drop in each case in convalescent samples to (3·5–4·7, mean 4·12 g/dl), (90–120%, mean 104%), respectively. Their AT3 were normal. FDPs were at the upper limit of normal (8 µg/ml n̄ < 8) in one early sample but otherwise normal. In two patients fibrinogen concentration was lower (2·4, 4·8 g/dl) acutely as was factor VIII (83, 91%), with a later rise to (4·5, 7·6 g/dl) and (108–140%), respectively. Their AT3 was low (63, 75%) and FDPs high (64, 16 µg/ml) acutely, returning to normal in the convalescent sample. In all patients platelet half life was moderately reduced (3·4–4·9 days, n̄ 5–6 days). Platelet aggregation was reduced acutely with ADP in six patients and collagen in five, but normal subsequently.

The results suggest that in the active stage of IE: (a) hypercoagulability may be caused by a rise in acute phase reactants, (b) subclinical consumptive coagulopathy may supervene and reverse this tendency, and (c) there is an unexpected reduction in platelet aggregation possibly as a result of continued circulation of previously activated "exhausted" platelets.

Enzymatic differentiation of cardiac and skeletal muscle

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Cardiac muscle differs from other striated muscle in preferred substrates. In normal myocardium energy is obtained primarily from lipid metabolism. To assess any differences in intracellular enzyme activities, 26 patients undergoing thoracotomy (13 for coronary artery bypass grafting, and 13 for aortic valve replacement) had right atrial appendage and intercostal muscle biopsy specimens taken before going on to bypass. Lipid and enzyme content was determined after a Folch extraction. Known diabetic and hyperlipidaemic patients were excluded. Lipid content was significantly greater in atrial muscle: triglyceride concentrations expressed as mean (SEM) were 308 (67) and 69 (14) μmol/g, respectively, $p < 0{\cdot}01$; non-esterified fatty acid concentrations were 0·84 (0·10) and 0·35 (0·05) μmol/g, respectively, $p < 0{\cdot}001$). In tissue homogenates enzyme activities (U/g wet weight) differed significantly. Glycolytic enzyme activity was lower in atrial muscle: hexokinase 1·19 (0·25) and 1·86 (0·15), phospho-fructokinase 0·44 (0·03) and 2·78 (0·03), pyruvate kinase 7·8 (0·4) and 14·3 (1·0), and glycerol 3 phosphate dehydrogenase 3·8 (0·2) and 15·2 (1·1), (all $p < 0{\cdot}001$). Enzymes of fat metabolism had significantly greater activity in atrial muscle: glucose 6 phosphate dehydrogenase 0·43 (0·03) and 0·20 (0·02), malic enzyme 0·16 (0·01) and 0·08 (0·01), 3 hydroxybutyrate CoA dehydrogenase 8·6 (0·5) and 3·8 (0·3), (all $p < 0{\cdot}001$).

These results support the increased importance of lipid metabolism and reduced role for glycolysis in cardiac muscle compared with other striated muscle.

Financial and resource considerations for initiating a coronary angioplasty service

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To date most cardiac centres starting coronary angioplasty have accommodated it within existing departmental facilities and resources. The cost and staffing requirements of such a programme are examined in this review of our four years experience in providing a regional coronary angioplasty service. From 1983 to 1986 a total of 243 procedures was performed at an estimated cost of £286 000 to the unit. This included actual expenditure in disposable angioplasty equipment (£126 000), additional nursing and technical staff (£63 000), and the cost of hospital stay (£97 000), but exclude the cost of six emergency bypass graft operations. The average cost of £1180 per procedure probably represents the minimum cost for coronary angioplasty without additional medical staff or capital cost of an interventional *x* ray laboratory. Our experience is that up to 150–200 angioplasty procedures may be accommodated in this way in a diagnostic cardiac laboratory by means of additional ancillary staff and rescheduling of diagnostic sessions.

As the indications for the procedure broaden it will almost certainly require purpose built interventional facilities, at which point the capital and staffing costs of the procedure will need further evaluation.

Does early β blockade reduce mortality in myocardial infarction by limiting infarct size?

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The mechanism by which acute phase β blockade reduces mortality in acute myocardial infarction is unclear. Therefore in a double blind placebo controlled study the effects of intravenous, followed by oral, metoprolol on peak serum lactic dehydrogonase (LDH) activity and aspartate aminotransferase (AST) activity, QRS score on ECG and thallium-201 (TL) perfusion defect score were studied in 129 patients with a median delay of 6·75 hours from the onset of symptoms of infarction. Peak LDH activity correlated with both QRS ($r - 0{\cdot}40$, $p < 0{\cdot}001$) and TL score ($r - 0{\cdot}44$, $p < 0{\cdot}001$), as did peak AST activity ($r - 0{\cdot}37$ and $0{\cdot}41$). While metoprolol did not affect these correlation coefficients it did influence the slope of regression lines, reducing peak LDH activity by 7% (90% confidence limits −475 to +199 iu) and peak AST activity by 11% (90% confidence limits −65 to +27 iu). Metoprolol did not reduce QRS score or TL defect size. Thus it appears that the reduction in enzyme release was not due to myocardial salvage.

It seems likely that the reduction in mortality after early intervention with metoprolol in myocardial infarction is due, not to limitation of infarct size, but to some other mechanism.

Cine magnetic resonance imaging of the cardiovascular system

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Cine magnetic resonance imaging using a field echo sequence with even echo rephasing has the same acquisition time as conventional static imaging (three minutes) but produces 40 ms frames representing an average cardiac cycle. It has three principal advantages: the integration of information from many parts of the cardiac cycle increases effective resolution, the high signal from blood aids the detection of intracardiac filling defects, and flow patterns can be assessed because of loss of signal from turbulent flow. We have used cine imaging in 100 patients and have identified four areas in which it is of particular value: (a) assessment of global and regional ventricular function can be made from a single oblique acquisition of approximately three minutes, and area length left ventricular volume measurements correlated well with the accurate multislice technique in 25 normal subjects and 20 with previous infarction ($r = 0{\cdot}96$ SEE = 10 ml); (b) filling defects such as thrombi ($n =$ three) and the intimal flap of aortic dissection ($n =$ three) were easily seen because of the high signal from blood and the lower signal from all other cardiac structures; (c) abnormal valve motion and the turbulent flow of valvar disease ($n = 30$) can be detected together with shunting through septal defects and surgical conduits ($n = 6$); and (d) the pericardium can be distinguished from pericardial fluid ($n = 4$), and the distinction between pericardial constriction and cardiac tamponade is simplified.

Cine imaging is an important advance that enhances the information from cardiovascular magnetic resonance studies in a large proportion of cases.

Rapid neointimal and medial hyperplasia after arteriovenous bypass in pigs

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Neointimal hyperplasia restricts flow and predisposes to thrombosis in coronary vein grafts. To investigate its mechanism and how it can be reduced, we established an experimental model in which a 3 cm long segment of autologous pig saphenous vein was grafted into a carotid artery. The vein was anastomosed end to end using bevelled ends and 7–0 continuous prolene sutures. Freshly isolated vein and grafts removed after one week were perfusion fixed at 100 mm Hg with 10% phosphate buffered formalin. A segment of freshly isolated vein and two to four segments from each graft were embedded in paraffin, stained with Van Gieson's elastic stain, and three transverse sections at each of three or four levels were analysed by computer aided planimetry using the endothelium, internal, and external elastic laminae to delimit the lumen, intima, and media, respectively. Cell viability was determined in extracts of unfixed vein and grafts frozen in liquid nitrogen by measurement of the ATP:ADP ratio. Freshly isolated vein ($n = 11$) had a luminal area of 2·1 (0·5) (SEM) mm^2, an intimal area of 0, a medial area of 0·7 (0·1) mm^2, and an ATP:ADP ratio of 3·3:0·1 ($n = 19$). Grafts after one week ($n = 7$) had a luminal area of 10 (1) mm^2, an intimal area of 0·4 (0·2) m^2, a medial area of 2·8 (0·4) mm^2, and an ATP:ADP ratio of 2·7:0·2 ($n = 14$). The data showed significant ($p < 0{\cdot}05$) increases in luminal, intimal, and medial cross sectional areas in grafted vein with maintenance of cell viability. Preliminary results on three grafts removed after one month showed further mean increases in intimal area to 2·6 mm^2 and in medial area to 5·5 mm^2.

The model thus reproduces the rapid intimal and medial proliferation seen in human coronary artery bypass grafts.

T wave normalisation on exercise: a non-specific finding after myocardial infarction

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Exercise induced ST segment shift is a marker for ischaemia in patients with heart disease. Following myocardial infarction, some patients do not exhibit ST segment shift despite developing effort angina, and a proportion of these 'normalise' inverted T waves on exercise. To ascertain the importance of such ECG changes, 11 patients who showed repeatable normalisation of T wave on symptom limited exertion (with no ST segment shift) underwent high resolution stress thallium-201 imaging, with simultaneous ECG recording of leads CM5 and CC5. In five patients the end point was angina; the remainder, fatigue or breathlessness. Seven patients had unequivocal Q wave infarction and the remaining four patients had documented myocardial infarction but without Q wave or ST segment change at the time of assessment. Four patients (all with Q wave infarction) had evidence of infarction on thallium scan with no reversible ischaemia, and none of these developed angina on stress. The remainder all had evidence of infarction and reversible ischaemia of variable severity. Of the remaining three Q wave infarcts, two had angina, and three of the four non Q wave infarcts who showed reversible ischaemia on thallium scanning stopped with angina.

We conclude that normalisation of the T wave as an isolated finding does not imply reversible ischaemia especially in the presence of Q wave infarction and is a non-specific finding after myocardial infarction.

Cardiorespiratory abnormalities to imagined psychological stress: assessment of vulnerability

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Situations of imagined psychological stress and exercise were suggested under hypnosis in 30 subjects (19 men; 11 women) using a previously published protocol. Continuous monitoring of three physiological variable were made. Fifteen patients had angiographically documented coronary artery disease (CAD), and 15 documented arrhythmias. Two personality questionnaires were completed. Twenty three (76·6%) patients had abnormal physiological responses to the psychological stress presented. Seventeen patients responded with hyperventilation, the mean fall in Petco2 was 13·9 (6) mm Hg compared with 5·1 (3·4) ($p < 0\,001$). Nine of these also had ECG abnormalities: SVT in three, ST elevation in one, ventricular bigemini in two, and ST/T wave abnormalities in three. Frequent extra systoles (> 10/minute) and bigeminy occurred in a further six patients in response to psychological stress. Seven patients developed hypocapnia at the thought of exercise; all had reproduced chest pain following a previous forced HV provo-cation test; CAD was present in six. An apologetic/self-effacing personality was significantly associated with physiological response to psychological stressors (emotion/exercise). This was associated with hostility in the patients with CAD and competitiveness in those with arrhythmias. The discriminant function score from the type A questionnaire predicted responders to psychological stress and exercise in the patients with CAD but not those with arrhythmias.

We suggest that it may be possible to determine groups of patients with heart disease who are particularly vulnerable to psychological stress.

Colour flow imaging of jet direction in aortic and mitral regurgitation: its clinical importance

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Colour flow imaging has provided new insights into spatial distribution of regurgitant flows. We evaluated the direction of aortic (AR) and mitral (MR) regurgitant flows to determine whether colour flow mapping can reveal consistent and specific patterns of spatial flow distribution. From a total of 87 patients, 63 had AR while MR was detected in 53. Twenty five patients had rheumatic heart disease (RHD); all had both AR and MR. AR was directed towards the mitral leaflet tip while the MR was directed posteriorly towards the left atrial back wall in all patients. Eight patients had congenital valve disease; six had bicuspid valve with jet direction along the mitral leaflet, and two had cusp fenestrations with jet directions toward the mitral valve tip. Nine patients had calcific aortic stenosis and mild to moderate AR, with jet directions along the anterior mitral leaflet ($n = 15$), mitral leaflet tip ($n = 3$), and anteriorly along the ventricular septum ($n = 1$). Twelve patients had AR secondary to collagen ($n = 2$), inflammatory disorder ($n = 6$), or dilated cardiomyopathy ($n = 4$). In all, the jet was rising from the cusp tips and was directed towards the mitral leaflet tips, similar to RHD. In six patients with anterior leaflet mitral prolapse the MR jet was directed immediately posteriorly. Conversely, in eight patients with leaflet mitral prolapse the jet was directed anteriorly against the posterior aortic wall. In patients with functional MR secondary to ischaemia ($n = 10$), or dilated cardiomyopathy ($n = 4$), jet direction was posterior, rarely exceeding 30% of the left atrium.

The flow direction together with the valve morphology is strongly indicative of the aetiology of the underlying disease except in calcific AR when the jet may follow any direction.

Single vessel coronary disease: what factors influence prognosis?

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Although single vessel disease (SVD) is often considered to have a relatively good prognosis, it is associated with increased mortality. In order to identify those at risk, a retrospective analysis of 884 patients with SVD was undertaken to ascertain which factors might predict death. All patients had had exercise stress tests and angiography. During a mean follow up period of 45 months 48 (5·7%) died, compared with 13 deaths (1·8%) in a group of 773 patients without significant coronary disease ($p < 0{\cdot}01$). Mortality in the SVD group was more common in the 330 patients with impaired left ventricular (LV) contraction (group 1) than among the 554 patients with normal LV function (group 2) (7·6% and 4·2%, $p < 0{\cdot}05$). Within group 1, mortality was higher among those patients with exercise induced ST depression(12 of 74), than among those without (13 of 256, $p < 0{\cdot}01$); exercise angina and exercise duration were not predictive. In group 2, mortality was greater in those patients who only reached stage 3 or less of a modified Bruce exercise protocol (19 of 288), compared with those who attained stage 4 or more (4 of 266, $p < 0{\cdot}01$). Neither exercise angina nor ST depression was predictive in this group. A history of severe angina was not associated with adverse prognosis in either group. In the groups at higher risk there was no difference in mortality between those treated medically and those treated surgically.

SVD patients have a higher mortality than those without significant coronary disease. High risk subgroups can be identified by means of exercise testing and the angiographic assessment of LV function.

Restenosis after coronary angioplasty: an analysis of stenosis morphology and the efficacy of repeat angioplasty

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Restenosis following successful percutaneous transluminal coronary angioplasty (PTCA) is an important clinical problem. Indeed in some patients PTCA may appear to accelerate the stenotic process. We have therefore examined stenosis morphology at restenosis, and reviewed the efficacy of repeat PTCA. Following 328 successful PTCA procedures, restenosis (to $> 50\%$ luminal diameter) was found in 70 patients. Angiographic records were available for retrospective analysis in 42 of these patients. The measured diameter stenosis before PTCA was 74 (12%) (mean (SD)) compared with 72 (14%) at restenosis (NS). The stenoses, however, were significantly longer at restenosis than at the initial procedure (8·6 (3·7) and 6 7 (2·4) mm, $p < 0{\cdot}01$). Furthermore in 52 patients who underwent repeat PTCA the trans stenotic pressure gradient was greater at restenosis than at the initial procedure (63 (26) and 56 (19) mm Hg, $p < 0{\cdot}01$). The angiographic success rate of repeat PTCA was 86%. Procedure related complications were two myocardial infarcts, one referral for emergency surgery, and one death.

These data indicate that at restenosis after PTCA lesions tend to be longer, suggesting that vascular trauma at the initial procedure often extends beyond the limits of the coronary stenosis. Nevertheless repeat PTCA can be performed with a high degree of success and without excessive complications.

Epicardial electrogram during angioplasty

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Endocardial recordings of monophasic action potentials (MAPs) provide a sensitive index of localised myocardial ischaemia registering changes during pacing to the angina threshold before the appearance of changes in the ECG or the onset of chest pain. Positioning of a MAP catheter on the left ventricular endocardium in the area of interest is not always technically easy or practical. We have appraised a MAP catheter on the right ventricular septum and an electrogram recorded from the angioplasty guide wire in the epicardial coronary artery. During balloon occlusion the electrograms registered ST depression and T wave changes that were readily quantifiable. Changes in the repolarisation of the MAP varied depending upon the position of the catheter. Our findings showed that the electrogram is useful in providing a sensitive, good quality, and easily obtainable signal using the guide wire which is already in position. The recording site, however, is limited to the course of the epicardial artery.

The MAP catheter enables examination of the electrophysiological changes in areas of the heart not directly influencing the electrogram. The combination of both the MAP and the electrogram, however, allows a flexible and comprehensive investigation of the myocardium during angioplasty.

Surface ventricular late potential activity in sustained and transient ventricular arrhythmias

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Surface ventricular late potential activity (VLPA) provides non-invasive evidence of slow conduction which is one of the prerequisites for reentry. We examined VLPA in 108 patients to study the mechanism of sustained and transient ventricular arrhythmias. Sixty two patients had recurrent sustained ventricular tachycardia that degenerated in some cases to ventricular fibrillation (group I), 21 suffered ventricular fibrillation during acute myocardial ischaemia (group II), 20 had non-sustained salvos of ventricular tachycardia (group III), and five had frequent premature ventricular complexes (group IV). Eighty one of the 108 patients had had previous myocardial infarctions, 12 had other cardiac disease, and 15 had "normal" hearts. VLPA occurred frequently in group I (50 of 62, 81%), but was less common in group II (7 of 21, 33%, $p < 0{\cdot}001$), in group III (3 of 20, 15%, $p < 0{\cdot}0001$) and in group IV (1 of 5, 20%, NS). Though evidence of slow conduction was found in most patients with sustained ventricular arrhythmias, it was not found commonly in patients with ventricular fibrillation and acute ischaemia, in those with non-sustained ventricular tachycardia, or in those with premature ventricular complexes.

Reentry may not, therefore, account for these transient ventricular arrhythmias. A difference in the mechanism of arrhythmogenesis may have important therapeutic implications.

Chronic second degree block: a comparison of surface ECGs, His bundle electrograms, and effort tests

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In 1982 we presented evidence to the society that chronic Wenckebach second degree block was not as benign as had always been thought. Subsequently it has been suggested that the standard ECG is inadequate for assessing the site of AV block and that His electrograms and exercise tests are required. We present data in patients seen in the Devon Heart Block and Bradycardia Survey. Eighty one patients were studied; 59 figured in our previous survival data and 22 were investigated subsequently. All had chronic second degree block, there were 26 with Wenckebach block (group I), 34 with Mobitz II block (group II), and 21 with fixed 2:1 or 3:1 block (group III). Fifty three patients had His electrograms, 38 being from groups I and II. In these the conduction delay was at the expected level in 30. It was paradoxical in three, multisite in five, and split His potentials were seen in two. A prolonged HV was the predominant finding in 15 patients from group III but a split His potential was seen in four. Fifty six patients had exercise tests, 45 coming from groups I and II. In these the change in conduction was in the expected direction in 17 and the reverse in three, but in 25 no change was recorded. In 11 patients from group III, conduction improved in one, deteriorated in six, and was unchanged in four.

In our patients the site of block indicated by the surface ECG usually coincided with that found on the His electrogram, and intrahisian block may mimic AV nodal delay but was only found in 10% of cases. Exercise tests proved of limited value as no change in conduction was recorded in about half of the patients.

Detection of superior limb and mid-baffle obstruction after Mustard's operation using spectral analysis of jugular venous Doppler signals

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Venous pathway obstruction after Mustard's operation occurs in about 10% of patients. It is usually suspected clinically and confirmed by angiography. Diagnosis using pulsed Doppler interrogation of the pathways and examination of the zero crossing output of the jugular venous Doppler signal has been reported. In view of inherent inaccuracies in the zero crossing technique we have used spectral analysis to evaluate the jugular venous Doppler waveform and its timing in association with the common carotid arterial signal obtained at the same site and displayed on a flow direction sensitive display. We have examined 47 of 67 survivors of Mustard's operation since 1974. Twelve have had correlative catheterisation including nine with baffle obstruction examined before and after relief by balloon angioplasty or surgery. In cases without evidence of obstruction the jugular venous signal has a biphasic waveform, the second component larger than the first, occurring synchronously with the diastolic phase of the carotid arterial signal. In nine patients with baffle obstruction (eight—superior limb, one—mid baffle) there was a change in the timing of the maximum venous component, becoming synchronous with the systolic peak of the carotid arterial signal, which normalised after relief. Severe venous turbulence ($n = 14$) was not an indicator of baffle obstruction. Spectral analysis of the jugular venous Doppler signal is a simple, rapid, reliable technique for detection of baffle obstruction. It has enabled us to detect superior limb obstruction in patients in whom it was clinically not suspected and at a stage when it was not so severe as to preclude balloon dilatation.

Ebstein's anomaly diagnosed in the first year of life: factors affecting mortality

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The outcome of 42 patients with Ebstein's anomaly symptomatic during the first year of life (mean age 6 days) was reviewed. All had tricuspid regurgitation. Congestive heart failure (CHF) and cyanosis were present in 22, cyanosis alone in 13, CHF alone in one, and serious arrhythmias in five. Systemic to pulmonary shunts were performed in seven, tricuspid annuloplasty in one (at 90 days), and tricuspid valve replacement (at 17 months) in one. Survival was 69% at 14 days, 52% at one year, and 37% at five years. Thirteen patients died within two weeks of diagnosis (mean age 5 days) all due to CHF or hypoxia. In the 14 patients who died later (mean age 2 9 years) sudden death occurred in eight. There were four surgical deaths (9%) (mean age 8 months). Univariate analysis of the clinical, anatomical, and histological factors leading to early death showed that age at presentation, hypoplasia—absence of trabecular and outlet portion of the right ventricle or both—small tethered leaflet, and associated anomalies were independent risk factors for early mortality. Quantification by computerised morphometric analysis showed that the right ventricular free wall fibrous content was significantly raised ($p < 0{\cdot}001$) compared with controls matched by age and size. Neither reduced wall thickness nor the increased right ventricular fibrous content, however, affected the time of death.

Early death is therefore strongly influenced by morphological but not histological features. Patients with favourable anatomy, however, are also at risk of sudden death, probably due to arrhythmias.

Peripheral pulmonary vascular and airway abnormalities in Indian adolescents with rheumatic mitral stenosis

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Lung biopsy specimens were taken from 15 adolescents (aged 11–21 years), when a mitral valvotomy was performed in Calcutta. They were examined by light, transmission, and electron microscopy. Abnormalities were most pronounced in the capillaries. They were embedded in dense connective tissue, and an increase in basement membrane material thickened the blood gas barrier. Intra-acinar arteries and veins showed an increase in muscularity and in adventitial connective tissue, with severe circumferential intimal fibrosis. Airway abnormalities were striking. The peripheral airways were encased and compressed by dense connective tissue and bronchial smooth muscle was increased. Six months after the mitral valvotomy was performed, the mean pulmonary arterial pressure had fallen from 42 to 23 mm Hg. Despite this satisfactory haemodynamic result, the long term effects of small airway compression on the growing lung indicate the need for early relief of mitral valve obstruction.

Adults with mitral stenosis may have persistent respiratory problems after valvotomy. Given our findings in young people, this may perhaps be attributed to the long term effects of the heart disease rather than chronic bronchitis as is often supposed.

Diastolic filling dynamics after intravenous verapamil in coronary patients

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We studied the effects of intravenous verapamil (V) on left ventricular (LV) pump function and diastolic filling dynamics. We gave V (0·1 mg/kg bolus followed by 0·005 mg/kg/min) to 10 patients four years after coronary bypass grafting and implantation of seven intramyocardial tantalum markers (MM). The studied patients had severe coronary artery disease. We simultaneously measured LV systolic (LVSP) and end diastolic pressure (EDP), positive dP/dt and τ, the time constant of isovolumetric pressure decay, by tipmanometry; cardiac index (CI) and coronary sinus blood flow (CSF) by thermodilution; and end diastolic volume (EDV), ejection fraction (EF), and peak diastolic filling rate (PFR) by MM filmed at 100 frames/second (biplane 30°RAO/60°LAO). Pressure volume relations were obtained in early, mid, and end diastole. V caused a slight but significant rise in EDP (11 to 14 mm Hg) and EDV (142 to 152 ml) and a fall in positive dP/dt (1748 to 1640 mm Hg/s), reflecting the drug's negative inotropic action. CI (2·7 and 2·9 l/minute) and EF (47 and 49%) did not decline due to LV unloading. Peripheral resistance decreased significantly (1496 and 1348 dyn s cm^{-5}) and CSF increased (88 vs 102 ml/minute). The speed of relaxation (63 and 62 m seconds) remained unaltered, and the pressure volume relation was shifted on the same curve to slightly higher values. PFR, however, was enhanced (269 to 334 ml/seconds).

Thus verapamil has little effect on systolic pump function, relaxation, and diastolic distensibility of the LV, but improves early diastolic filling. This improvement seems to be associated with an alteration in loading conditions due to peripheral vasodilatation or in part to a reduction in myocardial ischaemia due to an increase in coronary flow.

British regional heart study: an ECG assessment of risk

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As part of the British regional heart study, ECGs were recorded on 7735 men aged between 40 and 59 years. These ECGs were analysed by computer and coded results were transferred to a separate data base for statistical analysis. Follow up data on morbidity and mortality have now been obtained on each subject for at least five years and in some cases, up to seven and a half years. A new major ischaemic event—that is, acute myocardial infarction (MI), fatal or non-fatal—or sudden death was detected in 336 men during the follow up period. Non-fatal events accounted for over half the episodes (63%). Thirty five of those whose first event was non-fatal sustained a subsequent fatal event. ECG evidence of a previous MI carried over a five fold risk of a patient sustaining a further event, definite ischaemia carried a threefold risk while possible infarction and possible ischaemia carried a twofold risk compared with those with ECGs without such abnormalities. In a similar fashion, patients with LVH and secondary ST-T changes had over five times the risk of a future incident, whereas LVH without ST-T changes carried a twofold risk compared with those without such evidence. Overall, patients with any of these ECG abnormalities had twice the risk of a future event compared to those without such ECG changes whether or not they had other symptoms of ischaemic heart disease from the history.

In view of the fact that a high percentage of cases of myocardial infarction are silent and the ECG alone indicates the presence of secondary ST-T changes, it is concluded that the resting ECG has an important role in population screening.

Arrhythmias after recombinant tissue plasminogen activator in patients with acute myocardial infarction

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Arrhythmias (A) in patients following attempted thrombolysis (T) with recombinant tissue plasminogen activator (rt-PA) in the early phase of myocardial infarction (MI) are rarely documented. We monitored the ECGs continuously of 50 consecutive patients with MI (41 men, nine women; mean age 59 years, range 42–71) randomised to 20 mg, 50 mg, or 100 mg rt-PA on average 135 min after the onset of pain (range 20–240 min), and given intravenously over 90 minutes. At 90 minutes infarct related vessel patency was assessed by coronary angiography and graded 0–3 (TIMI) reperfusion. Forty one patients received a further 50 mg rt-PA over five hours and in seven it was over one hour. In 48 patients, intravenous heparin was given immediately after rt-PA. At the start of rt-PA all patients were in sinus rhythm although three had had third degree AV block when first seen. Following rt-PA 39 patients had ≥ 1 major A during out of hospital and in hospital observation. Twenty patients had ≥ 1A during the 90 min rt-PA infusion: four patients developed ventricular fibrillation (VF) (one during cardiac catheterisation), two patients had idioventricular rhythm (IDVR), self terminating ventricular tachycardia (self term VT, defined as five or more consecutive ventricular ectopics) and runs of ventricular bigeminy in eight, atrial fibrillation (AF) in two patients, transient 2:1 AV block in one patient, nodal rhythm (NR) in three patients, and sinus bradycardia in two. Five of these 20 patients received 20 mg rt-PA, nine 50 mg, and six 100 mg: eight had grade 3, four—grade 2, four—grade 1 and four—grade 0 reperfusion. Of the seven patients subsequently receiving 50 mg rt-PA over one hour, one developed IDVR and NR. Of the 41 patients receiving it over five hours, two patients developed VF, nine IDVR, and six self term VT. Between the end of rt-PA and discharge from hospital 12 patients had self term VT, nine patients had IDVR, and three AF. Late VF did not occur and 46 survived hospital treatment.

The overall incidence of VF (12%) is similar to that in patients with MI not undergoing thrombolysis.

Factors influencing the perception of pain in exercise induced myocardial ischaemia after acute myocardial infarction

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Eighty five patients underwent modified Bruce protocol exercise testing two weeks and three months after documented myocardial infarction. Twenty five of 85 (30·1%) had ST segment depression (>1 mm) on both occasions. Chest pain (CP) accompanied the ECG changes in 13 of 25 (13·2%); in 12 of 25 (15·7%) ST depression was asymptomatic (ASY). No patient was diabetic. Baseline measurements of age, sex, smoking, site of infarction, ejection fraction, and enzyme rises were not significantly different among the groups. At two weeks, exercise length was 8·5 (4·9) (CP) and 10·0 (3·3) (ASY); at three months, exercise length was 10·0 (5·1) and 13·9 (1·9), ($p < 0.06$), respectively. Patients with angina scored significantly higher on an illness behaviour questionnaire ($p < 0.03$) and in particular on the hypochondriasis index ($p < 0.05$) and anxiety depression scales ($p < 0.03$). Forced hyperventilation reproduced chest pain in seven patients, six with exercise induced chest pain and one without ($p < 0.05$); there was a greater mean fall in Petco$_2$ at two weeks but not at three months on approach to exercise in patients who subsequently sustained chest pain. A significantly higher life event stress score in the months before infarction was found in the subjects with chest pain ($p < 0.04$).

Patients who perceive pain on exercise with ST segment depression recognise more life events as stressful and have a greater anxiety and somatic awareness than patients who do not. Interestingly patient assessment of quality of life was not significantly different although relative assessment was persistently lower in the chest pain group.

Clinical and angiographic predictors of acute coronary occlusion at coronary angioplasty

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Acute coronary occlusion is a major complication of coronary angioplasty (PTCA) and if not successfully redilated leads to myocardial infarction (MI) or necessitates coronary artery bypass grafting (CABG). To identify risk factors for this complication in a consecutive series of 234 patients undergoing PTCA we have analysed retrospectively the clinical features and coronary stenosis morphology (length, severity, and eccentricity) of 29 patients who had acute occlusion at PTCA (group I), of whom 15 went on to develop a procedure related MI. Twenty nine patients matched for target vessel disease who underwent an uncomplicated procedure served as controls (group II). Group I had significantly longer coronary stenoses than group II (mean length 13·6 mm and 10·3 mm; $p = 0.005$). The severity of stenoses was similar in both groups as was the incidence of eccentricity. In the subgroup of patients, however, who could not be successfully redilated and therefore had a procedure related MI, there was a significantly higher number of eccentric stenoses compared with those who were successfully redilated (nine of 15 and two of 14; $p < 0.02$). This group also had a significantly higher number of patients with remote previous MI (13 and five; $p < 0.01$).

We conclude that longer stenoses are more likely to occlude at PTCA, and if eccentric, redilatation is frequently unsuccessful leading to a procedure related MI. The risk of this occurring is also high in presence of a previous remote MI. Risk assessment before PTCA should take into account the above angiographic and clinical characteristics.

Renin angiotensin aldosterone system and posture in the response to diuretics in cardiac failure

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Bed rest promotes a diuresis in patients with oedema and the response to intravenous diuretics is greater in the supine position compared with the upright position. It is thought that this effect is due to the increased activity of the renin angiotensin aldosterone system during upright posture. To test this hypothesis we have studied the effect of bumetanide 1 mg given intravenously to 10 patients with cardiac failure established on enalapril, in the upright and supine positions. Control blood samples were drawn for the measurement of plasma renin activity and plasma concentrations of angiotensin II and aldosterone after one hour of supine rest. Subjects then emptied their bladders and were given bumetanide 1 mg intravenously. They were then assigned to upright or supine posture, and all urine was collected for the next four hours and further blood sampling took place at 60, 120, and 240 minutes after the injection. Each subject had studies in both upright and supine positions. With the subjects supine urine output was 834 (94) ml and sodium excretion 85 (14·5) mmol; when upright urine output was slightly lower at 728 (99) ml ($p > 0{\cdot}05$), and sodium excretion was 76 (15 mmol) ($p > 0{\cdot}05$). Glomerular filtration rate was lower in the upright (86 (24) ml/minute) than in the supine position (112 (24) ml/minute) ($p > 0{\cdot}05$). There was no difference in plasma renin activity and angiotensin II concentration in either position even though there was an increase in plasma aldosterone in the upright position.

We conclude that converting enzyme inhibition blocks the expected effect of posture on diuretic therapy.

Subtherapeutic dosing of flecainide as a provocative test for non-inducible ventricular tachycardia

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Induction of clinical ventricular tachycardia (VT) is important during an electrophysiology study in order to map its origin. Flecainide acetate at low blood concentrations shortens the effective refractory period of Purkinje fibres but prolongs that of the ventricular muscle. This disparate change in effective refractory period may exaggerate heterogeneity in recovery of excitability and allow reentry. Slowing of conduction by flecainide may perpetuate reentry in susceptible patients. Eleven patients (mean age 56 years, range 19–70) with previously documented sustained VT (cycle length 343 (62) mean (SD)), range 280–480 ms were studied. A 12 lead electrocardiogram during clinical tachycardia in seven patients showed left bundle branch configuration and in three a right bundle branch pattern. In one patient clinical VT was multiform. The ventricular stimulation protocol, consisting of sinus rhythm or a drive of 100, 120, or 140 bpm plus one, two, or three ventricular extrasystoles delivered to the right ventricular apex, did not provoke arrhythmia in any patient. Flecainide acetate (1 mg/kg) was given intravenously over five minutes. The stimulation protocol was repeated 10 minutes after the start of the administration. In four (36%) patients sustained VT could be induced by a drive cycle (in two patients at 120 and other two at 140 bpm) and two ventricular extrasystoles. In three patients the configuration and mean rate of induced VT, as identified by a 12 lead electrocardiogram, was identical to the previously documented spontaneous clinical VT. In one patient a faster non-clinical arrhythmia was induced. With this dose of flecainide acetate the ventricular effective refractory period increased from 243 (21) to 256 (22) ms ($p < 0{\cdot}01$).

Thus, in patients with VT in whom routine electrical stimulation fails to provoke arrhythmia, repeat stimulation after a subtherapeutic doses of flecainide might be used as a provocative test.

Serum cortisol concentrations in myocardial infarction are predictive of prognosis

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Serum cortisol concentrations are raised in acute myocardial infarction but not in angina. We have studied prospectively the time course of the cortisol, creatine kinase (CK), and CK–MB response to myocardial infarction. In 70 patients admitted within six hours of an acute myocardial infarction blood was taken at presentation, then four hourly over the next 36 hours and then at 48, 60, and 72 hours. The samples were centrifuged and serum stored at

−70°C. Serum cortisol concentrations were highest on admission 968 (340) µmol/l (mean (SD)) and fell slowly over the next two days. Serum CK and CK-MB concentrations at presentation were 318 (668) U/l and 36 (63) U/l respectively and reached peak concentrations at 12–16 hours (2486 (1627) and 334 (224) U/l respectively). The cortisol and CK–MB concentrations correlated poorly at presentation ($r = 0\cdot22$). However, peak CK–MB correlated with peak cortisol concentrations ($r = 0\cdot53$, $p < 0\cdot001$). Five patients died within 10 days. There was no difference in initial (36 (63) and 36 (23) U/l), or peak (334 (224) and 559 (322) U/l) CK–MB concentrations between those surviving and those dying. In those who died, however, cortisol concentrations were significantly higher both at presentation, 1448 (423) and 931 (309) µmol/l, ($p < 0\cdot01$) and at peak levels, 2317 (795) and 1094 (450) µmol/l, ($p < 0\cdot001$). Only one patient who died had a peak cortisol below 2000 µmol/l. Of the survivors only two had peaks above 2000 µmol/l, giving this concentration predictive value for mortality of 60%, sensitivity 80%, specificity 96%, and an accuracy of 95%.

Serum cortisol concentration is raised earlier in the course of infarction than CK and CK–MB and shows a greater predictive value for prognosis. These features may be of value in early intervention studies in myocardial infarction.

Enhanced granulocyte aggregation responses after acute myocardial infarction

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University Department of Medical Cardiology, Royal Infirmary, Glasgow

Raised white cell count is an accurate predictor of myocardial infarction (MI) and stroke, and also correlates with risk of recurrence and mortality in these diseases. Thus it has been proposed that leucocytes have an important role in the pathogenesis of ischaemic vascular disease. Using a recently developed whole blood aggregation assay, granulocyte function in 12 patients with acute MI was compared with results from 12 normals matched for age, sex, and smoking habit. White cell count (WCC) and differential were also measured. Samples were taken within six hours of onset, and MI was confirmed by ECG and enzyme changes. The aggregation response of granulocytes to the chemotactic tripeptide nFMLP (40 µmol/l) was significantly greater in the MI group ($p < 0\cdot0001$), as were the total WCC, and the granulocyte count (both $p < 0\cdot0001$). No correlation between WCC and aggregation was observed, and adjusting the granulocyte count by diluting with buffy coat free blood did not reduce the granulocyte response. Thus blood from MI patients contains large numbers of aggregatable granulocytes. Such cells are liable to become sequestered in the microcirculation promoting ischaemia by physically impeding flow and causing tissue damage by the release of toxic oxygen metabolites.

Whether this is of aetiological importance is uncertain but it is plausible that further myocardial damage will be caused in this manner after the acute event. Infarct size has been measured as part of the study and will be compared with the granulocyte function data.

Ischaemic left ventricular dysfunction: frusemide or nitrate?

Ann Tweddel, W Martin, I McGhie, I Hutton
University Department of Medical Cardiology, Royal Infirmary, Glasgow

In patients with myocardial ischaemia the acute effects of intravenous (IV) frusemide, with increased systemic vascular resistance may be detrimental, and treatment with nitrate may be more appropriate. Eighteen patients were studied with ischaemic left ventricular dysfunction (EF less than 30%); eight randomly received frusemide 40 mg IV, and ten isosorbide mononitrate (ISMN) 15 mg. Coronary and systemic haemodynamics were measured and myocardial nutrient flow assessed by xenon washout. With ISMN blood pressure was unaffected, whereas with frusemide systolic, diastolic, and mean arterial pressure increased at 30 min (91 (4) to 104 (6) mm Hg). Because cardiac index fell at 30 min with ISMN (2·71 (0·12) to 2·33 (0·17), ($p < 0\cdot02$)) and was unchanged with frusemide (2·55 (0·13), 2·53 (0·14) l/minute/m^2), with both treatments the calculated systemic vascular resistance increased, with ISMN by 17% (1578 (186) to 1844 (255), $p < 0\cdot05$) and with frusemide 14% (1574 (148) to 1786 (180) dyn.s.cm^{-5}, $p < 0\cdot02$). Nitrate produced no significant change in coronary sinus flow (119·7 (13·1) to 108 (17·7) ml/minute) nor in myocardial nutrient flow, but oxygen extraction decreased with a narrowing arteriovenous oxygen difference (11·9 (0·83), 10·4 (0·68), and 10·7 (0·73) vol% at 30 minutes, $p < 0\cdot02$). In contrast, with frusemide coronary sinus flow increased (130·3 (11·6) to 170 (25) ml/minute, $p < 0\cdot05$), extraction was unchanged and myocardial nutrient flow increased from the left coronary injection (54·7 (5·4), to 67·6 (4), $p < 0{\cdot}05$) but was unchanged for the right coronary injection (45·4 (6·6) to 39·2 (4·8) ml/minute).

These results suggest that despite the increased systemic vascular resistance, coronary haemodynamic function is not adversely affected by frusemide and there would be little advantage in using nitrate.

Post cardioversion ventricular arrhythmias in patients taking digoxin

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Clinical and experimental evidence suggests a risk of inducing malignant ventricular arrhythmias when digoxin toxicity is present. Recent studies did not show any increase in ventricular arrhythmias if the serum level of digoxin was normal. It has been inferred that in the absence of evidence of digoxin toxicity, cardioversion could proceed safely. To test this hypothesis a retrospective study was carried out comparing the occurrence of ventricular arrhythmias in a group of patients on digoxin at the time of cardioversion with a group who were not (controls). Eighty three elective direct current cardioversions were performed for atrial tachyarrhythmias (80 men, mean age 54 years). Fifty patients were taking digoxin (40 taking 0·25 mg daily) and received their last dose 23 (14) hours before cardioversion. None had clinical or electrocardiographic evidence of toxicity, and digoxin concentrations were not measured. Immediate post cardioversion ventricular arrhythmias (bigemini, multifocal ectopics, and non-sustained ventricular tachycardia) occurred in 10 of the 50 patients on digoxin and one of the 33 controls, $p < 0{\cdot}05$. Multivariate analysis of other variables showed that digoxin was independently correlated with the occurrence of arrhythmias, $p < 0{\cdot}05$. Arrhythmias tended to occur more frequently in patients on digoxin 0·5 mg daily or if the last dose was within 12 hours of cardioversion, p = NS.

There was a higher incidence of potentially malignant ventricular arrhythmias following cardioversion in patients on digoxin compared with controls. Caution is advised when cardioverting digitalised patients even those apparently non-toxic.

Changes in left ventricular performance after coronary artery surgery

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The serial effects of myocardial revascularisation on left ventricular performance were assessed using echocardiography and symptom limited treadmill exercise testing in 54 patients. Before coronary artery surgery (CAS) 35 patients had had at least one myocardial infarction, 19 had moderate, and nine had severely abnormal left ventricular function shown angiographically; 48 patients had multivessel coronary artery disease. Up to six months after CAS, there were no significant changes in left ventricular end diastolic diameter although percentage left ventricular fractional shortening decreased significantly at one month (31·0% and 28·8%, $p < 0{\cdot}05$), but not thereafter. There was a significant increase in the incidence of new left ventricular wall movement abnormalities after CAS; 77% of the patients developed anteroseptal hypokinesia with coexistent posterolateral hyperkinesia 10 days postoperatively, but the frequency of this decreased to 31% by six months. Exercise haemodynamics, exercise duration, and features of reversible myocardial ischaemia all improved progressively and significantly after CAS. No patient sustained a CAS related myocardial infarction and there were no changes in electrocardiographic R wave amplitudes during follow up.

We conclude that new abnormalities in left ventricular wall movement develop quite commonly early after CABG but usually resolve by six months and do not seem to influence exercise performance or haemodynamics.

Evaluation of myocardial tomography by thallium-201 in patients with chest pain

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Exercise thallium imaging is an accepted technique for the evaluation of patients with chest pain suspected of having coronary artery disease. The application of tomography to this technique should further increase its accuracy. Thirty two patients undergoing coronary arteriography for symptoms suggestive of angina have been studied using exercise tomographic thallium scanning. Patients were exercised to a symptom limited end point on a bicycle ergometer. ECG monitoring and recording was performed throughout. Seventy five MBq of thallium-201 was injected one minute before the end of exercise. Tomographic imaging was performed immediately following exercise. Thirty two images were acquired over a 180° arc (time per image 40 seconds) and displayed on a 64 × 64 matrix. Sections were reconstructed parallel to and perpendicular to the long axis of the left ventricle. Fifteen patients had ECG evidence of previous myocardial infarction; thallium tomography identified 12 of these, and incorrectly identified seven further patients (sensitivity 80% specificity 59%). Twenty five of the 32 patients had angiographic evidence of coronary disease not related to infarct areas; thallium tomography identified all of these and incorrectly identified two normal subjects as having a reversible defect (sensitivity 100% specificity 71%). It was also possible to identify correctly which coronary arteries were affected. Thallium tomography correctly identified 46 major coronary stenoses but did not detect nine less severe lesions.

Exercise thallium tomography is an accurate technique for identifying patients with coronary artery disease and can be used to identify which coronary arteries are diseased.

Magnetic resonance measurement of aortic compliance

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Arterial compliance has previously been difficult to measure non-invasively, and its importance in the assessment of vascular disease and as a component of left ventricular afterload is unknown. We have used magnetic resonance to study changes with age in regional aortic compliance and in total arterial compliance. Twenty normal volunteers were studied, age range 16 to 71. Sections 10 mm thick were taken in three oblique planes perpendicular to the mid points of the ascending aorta (AA), the aortic arch, and the descending thoracic aorta (DA). Volume changes between diastole and systole were calculated from the change in area, and compliance was derived using the pulse pressure measured with a sphygmomanometer. Total arterial compliance was calculated from the left ventricular stroke volume measured by summing chamber areas in multiple contiguous slices. Mean (SD) normal compliance in ml/mm Hg was: AA 0·031 (0·018), arch 0·020 (0·012), DA 0·014 (0·007), and total compliance 1·46 (0·35). Ascending aortic compliance was significantly higher than at the other sites ($p < 0{\cdot}001$). There was a strong correlation between compliance and age for all three sites ($r = -0{\cdot}76$ AA, $-0{\cdot}83$ arch, and $-0{\cdot}71$ DA), but there was decreasing dependence upon age more distally (slope = -77 AA, -56 arch, -38 DA, $\times 10^{-5}$).

We conclude that regional aortic and total arterial compliance can be measured non-invasively by magnetic resonance. The ascending aorta is the most compliant region of the aorta and normal compliance falls with age. The importance of these results for patients with cardiovascular disease remains to be determined.

Pulmonary artery blood flow patterns studied by magnetic resonance

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Magnetic Resonance Unit, National Heart and Chest Hospitals, London

Pulmonary artery flow can be studied non-invasively by cine magnetic resonance velocity mapping, and it is potentially of interest in a variety of disorders. We have studied 25 normal subjects and three patients with pulmonary arterial hypertension, and compared their aortic flow and left ventricular output measured from ventricular volumes. Pulmonary artery distensibility has also been measured from changes in cross sectional area during the cycle There was plug flow during most of systole with a small channel of reverse flow beginning just before pulmonary valve closure. The normal two dimensional velocity profile was skewed, but the direction of skew varied between individual subjects and throughout the cycle. Two centimetres above the pulmonary valve the dominant direction of the skew was posterior, but immediately below the bifurcation it was anterior. There was no regular pattern in two subjects. Pulmonary flow, aortic flow, and left ventricular stroke volume showed close agreement ($r = 0{\cdot}96$, SEE = 8 ml), validating the technique and suggesting a method for the measurement of intracardiac shunting. In the patients with pulmonary hypertension, pulmonary flow was reduced and there was an earlier and more extensive channel of reverse flow. Pulmonary artery distensibility (fractional change in area) was 0·07 (normal 0·25 to 0·30).

These studies validate magnetic resonance pulmonary artery velocity mapping and illustrate potential sources of error in Doppler flow measurements. The abnormalities in patients with pulmonary hypertension suggest that the technique may be of value in such patients, but futher studies are indicated.

Cross sectional echocardiography in cardiac hydatidosis

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Cardiac hydatidosis is rare, is curable by operation, and must be differentiated from cardiac tumours. We present the cross sectional echocardiographic findings in six patients with cardiac hydatidosis who subsequently underwent operation with pathological examination of the excised specimen. The patients were aged 20–59, median 37 years; there were five men and one woman. In addition, none had hepatic but five had pulmonary hydatidosis with pulmonary hypertension (mean pulmonary artery pressure >36 mm Hg). Echocardiography showed at least one large cyst in the left ventricular myocardium in five patients: in two this involved the anterior septum, in another two the cysts were in the inferior wall, and one of the patients had a grossly deformed apex of the left ventricle. In another patient the cyst was in the septum and had ruptured into the pericardial space. In the patient without left ventricular involvement, the cyst was attached to the posterior wall of the right atrium and had two pedunculated daughter vesicles which crossed the tricuspid valve into the right ventricle during diastole. Surgical pathology confirmed the echocardiographic appearances of non-homogeneous cavitations with calcifications.

Cross sectional echocardiography was useful in the identification and preoperative localisation of the cysts in these patients with cardiac hydatidosis.

Differential effects of acetylcholine on conductance and resistance vessels in patients with angiographically normal epicardial coronary arteries

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Acetylcholine (ACh) has been shown to be a weak dilator of angiographically normal human coronary arteries in vivo, but constricts atherosclerotic segments. The effect of ACh on small resistance vessels has been less well documented. We studied eight patients aged 38–68 years with chest pain and normal coronary arteriograms but no myocardial ischaemia inducible by exercise or provocation tests for spasm. After diagnostic angiography, normal saline was infused at 1 ml/minute into the left coronary artery for three consecutive two minute periods, followed by intracoronary ACh from 10^{-7} mol/l to 5×10^{-3} mol/l. Angiography was repeated after each infusion. Changes in left anterior descending (LAD) artery calibre were measured by computerised analysis. In three patients, changes in coronary blood flow during each infusion were assessed by the indirect Fick principle from changes in coronary sinus oxygen saturation (CSo_2). No significant changes in LAD calibre or CSo_2 occurred with infusions of normal saline. ACh from 10^{-7} to 10^{-4} M caused a small dose dependent dilatation of the proximal LAD in six patients, maximum 7·2 (6)% (mean (SD), $p=0{\cdot}05$), but a large increase in CSo_2 corresponding to an estimated flow increase of 367 (57)%. From 10^{-3} mol/l to 5×10^{-3} mol/l, ACh caused diffuse constriction of the LAD in six patients, maximum 21·3 (17)%, ($p=0{\cdot}001$) which was associated with angina and ischaemic ST changes. Constriction followed dilatation in four patients.

These data suggest that intracoronary ACh can cause both dilatation and constriction of the same segments of angiographically normal epicardial coronary arteries in man, dependent on dose. It also causes massive dose dependent increases in total coronary blood flow.

Amiodarone: effects on colour vision

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York District Hospital, York

Amiodarone is a commonly prescribed drug used to control cardiac arrhythmias. An unwanted and universal side effect is corneal microdeposits visible with the slit lamp corneal microscope. An open question is whether amiodarone affects colour vision by either microdeposits or retinal insult. We studied the colour vision of 14 patients on amiodarone and 13 control patients. The tests of colour vision we used were those recommended by the international research group on colour vision deficiencies. The results show that there is no significant difference between the two groups on the Farnsworth-Munsell 100 hue test, the mean square root error scores (SD) being: control: 12·69 (5·21); amiodarone: 11·27 (4·23). On the more sensitive Pickford Nicolson anomaloscope, however, the amiodarone group required significantly ($p<0{\cdot}05$) more blue in the blue green match than the control group. This result would be expected in an acquired defect of colour vision showing a tritanopic (blue/yellow)axis. A correlation between time on amiodarone and the amount of blue required in the blue green match shows that the two variables are inversely correlated ($r=-0{\cdot}68$, $p<0{\cdot}02$);—that is, the anomaloscope settings of the amiodarone group become more similar to those of the control group with increasing time on the drug. This suggests that amiodarone has an initial disruptive effect on colour vision that disappears over time (our results show that the critical duration is about twelve months).

We emphasise that the effects of amiodarone on colour vision are subtle and likely to be missed by most conventional tests of colour vision.

Cardiac function and anatomy after Mustard's operation for transposition of the great arteries

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R H Klipstein, H Bogren, D B Longmore
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Mustard's operation for transposition of the great arteries redirects the circulation at atrial level and it has been used successfully since 1964. Many patients have now reached adult life, but ventricular function and tricuspid competence are important determinants of late morbidity. We have investigated magnetic resonance imaging in the assessment of cardiac anatomy and function in 17 adults, nine to 20 years after operation. The connections and anatomical associations of the great arteries were clearly visible in all cases. Five patients had residual ventricular septal defects which, with the exception of one small defect, were easily seen. The intra-atrial baffle was best seen in transverse slices, and the systemic venous connection showed as a fairly narrow channel lying in the posterior part of the cavity. The pulmonary venous connection was best seen in the coronal slices. Ventricular volumes were measured by adding areas in multiple contiguous sections, and the right to left ventricular stroke volume ratio was used as a measure of tricuspid regurgitation. Ejection fractions measured by radionuclide ventriculography were lower than the magnetic resonance measurements, and the correlation for the left ventricle was closer ($r=0{\cdot}75$) than for the right ($r=0{\cdot}49$). There was a significant difference between the mean right to left ventricular stroke volume ratio in those with Doppler echocardiographic evidence of tricuspid regurgitation (1·81) compared with those without (1·16), (normal range 0·8 to 1·2).

Magnetic resonance imaging is a useful adjunct in the postoperative follow up of patients who have had Mustard's operation for transposition of the great arteries.

In vitro validation of assessment by Doppler ultrasound of the supra-annular (6650) and standard (6625) Carpentier-Edwards mitral prostheses

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In native mitral valves, pressure half time ($T\frac{1}{2}$) is fairly independent of flow compared with peak left ventricular inflow velocity (Vmax). This has not been validated for prosthetic valves. We therefore measured and compared Vmax, $T\frac{1}{2}$, and actual orifice area (OA) for three unimplanted Carpentier-Edwards valves (model 6650 sizes 31 and 29 mm, model 6625 size 29 mm) and one explant (model 6625 29 mm). We used a computer controlled positive displacement pulse duplicator with 20 rate/stroke volume combinations (diastolic mean flow 3·1–16·9 l/minute). Doppler recordings were made with a Vingmed SD 50 and valve opening was recorded with a video camera. Vmax, $T\frac{1}{2}$, and OA all varied with flow. $T\frac{1}{2}$ was independent of stroke volume, but directly proportional to diastolic time interval. Alterations in the shape of the drive waveform, used to model ventricular compliance changes, affected $T\frac{1}{2}$ independently of diastolic time interval. There was no significant difference in $T\frac{1}{2}$ among the valves and $T\frac{1}{2}$ did not correlate with observed orifice area. Both Vmax and OA were directly proportional to rate and stroke volume and there was a correlation between OA and Vmax. The valves were significantly different in terms of Vmax ($F=38$; $p<0{\cdot}0001$) and OA ($F=12$; $p<0\ 0001$). Ranges for OA were 0·5–1·8 cm^2 (6650 31 mm); 0·6–1 6 cm^2 (6650 29 mm); 0 4–1·6 cm^2 (6625 29 mm); and 0·3–1·3 cm^2 (explant 29 mm).

For Carpentier-Edwards mitral prostheses in vitro, $T\frac{1}{2}$ is dependent on the shape and duration of the ventricular filling curve. This suggests that in vivo, $T\frac{1}{2}$ should be related to heart rate and ventricular function. Vmax is better than $T\frac{1}{2}$ as an indicator of orifice area.

Determinants of cardiac reserve after intra-atrial repair of transposition of the great arteries

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Hospitals for Sick Children, Great Ormond Street, London

Patients after intra-atrial repair of transposition of the great arteries are at risk of sudden death, especially during exercise. We used continuous wave Doppler to investigate the association of heart rate and stroke volume index during supine exercise in 36 patients without symptoms, 14 who had had a Senning operation [age range 6–15, mean 8·4 years] and 22 who had had a Mustard operation, age range 6·9–28, mean 15·9 years]). Resting heart rate, stroke volume index, and cardiac index were similar in both groups. The pattern of stroke volume index response during exercise was normal in the young patients ($\leqslant 12$ years after surgery) with no significant differences between those who had had the Mustard and those who had had the Senning operation. In 16 older (Mustard) patients (11–23 years after surgery), however, cardiac index was significantly reduced ($p<0{\cdot}05$) due to a significant reduction in peak exercise stroke index volume (43 (8) ml/beat/m^2 in Mustard, 55 (4) ml/beat/m^2 in normal, $p<0{\cdot}001$). In eight of 16 patients stroke volume index fell by 20% or more compared to an average increase of 6% in normals. Heart rate responses were not significantly different.

Older patients after the Mustard operation do not have stroke volume index reserve to maintain cardiac index during exercise. A precipitous fall in stroke volume index may develop during rapid heart rate, and place the patient at risk.

Exercise capacity and symptoms are objectively improved by an activity sensing pacemaker (Activitrax)

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Lesley Ludgate, Trudy Lowe, S C Webb,
D M Krikler
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Atrial tracking pacemakers may improve exercise capacity and symptoms because they maintain atrioventricular synchrony and preserve the physiological heart rate response to exercise. A rate responsive pacemaker which reacts to "physical activity" (VVI-Activitrax (Act)) may be effective in patients with sinus node disease who are unsuitable for VDD pacing. We performed a double blind randomised acute and chronic cross over study in 10 patients ages 30–75 years, at least three months after implant, who had complete atrioventricular block at rest and during exercise using a modified Bruce protocol. We assessed symptoms related to breathlessness, fatigue, and psychological state using a visual analogue scale questionnaire, and exercise capacity (maximal oxygen consumption and anaerobic threshold) during VVI-Act (peak rate 125/minute) and conventional fixed rate VVI pacing (70/minute). One month after randomisation treadmill exercise was performed. The mode was then changed to the other pacing mode and exercise repeated three hours later. After another month the process was repeated but in the reverse order. During chronic assessment there was subjective improvement of breathlessness and fatigue with VVI-Act pacing ($p<0{\cdot}05$). During acute assessment maximal oxygen consumption (ml/kg/minute)increased and the benefit was maintained during chronic VVI-Act and chronic VVI pacing: 18 (1), 19 (1), and 16 (1), ($p<0{\cdot}02$). Oxygen consumption (ml/kg/minute) at the anaerobic threshold likewise improved: 14 (1), 14 (1) and 12 (1), ($p<0{\cdot}04$).

Activity detecting rate responsive pacing is thus superior to fixed rate ventricular pacing in patients with complete AV block.

Br Heart J 1988;59:145

Correspondence

Tricuspid atresia with transposition of the great arteries in adolescents and adults: current state and late complications

Sir,
In their recent article (1987;57:543–7) on tricuspid atresia with transposition of the great arteries Warnes and Somerville emphasised the importance of subaortic stenosis in these patients, especially those with coarctation. They suggested that the Fontan procedure was the procedure of choice in these patients but remarked that in patients with subaortic stenosis the prognosis after Fontan surgery is very poor.

I recommend a combination of a modified Damus-Stansel-Kaye operation[1] and the Fontan operation in patients with tricuspid atresia with transposition of the great arteries, especially when there is appreciable subaortic stenosis that must be bypassed. I believe that this combination gives better emptying of the left ventricle and prevents the development of a poorly compliant left ventricle, pulmonary hypertension, and increased right atrial pressure that can cause deterioration and death after the Fontan procedure.

During my recent sabbatical year at the Hershey Medical Center, Pennsylvania, when I worked with Dr John Waldhausen and Dr Jack Meyers, we used this technique very successfully in a few patients with tricuspid atresia and transposition of the great arteries. In newborn babies with this anomaly (in whom the Fontan procedure is impossible) instead of banding the pulmonary artery we dissected the proximal pulmonary artery and anastomosed it to the ascending aorta; a shunt to the branching pulmonary artery was achieved by a modified Blalock-Taussig technique with a 4 mm Goretex graft. We planned to perform a Fontan procedure when these patients were older, after disconnecting the Blalock-Taussig shunt.

Joram Glaser,
Paediatric Cardiology Unit,
Shaare Zedek Medical Center,
Jerusalem, Israel.

Reference

1 Glaser J, Castaneda A. A new variation of the Damus-Stansel-Kaye procedure for correction of the Taussig-Bing anomaly *J Thorac Cardiovasc Surg* 1983;**86**:157.

This letter was shown to Dr Somerville, who replies as follows:

Sir,
I was interested in Dr Glaser's recommendation that a combination of modified Damus-Stansel-Kaye and the Fontan operation should be used to treat patients with tricuspid atresia and transposition of the great arteries with significant subaortic stenosis. Technically virtuoso operations are always attractive and appear, on some occasions, to have short term benefits. But I doubt whether this operation will produce good long term survival into adolescence or adult life, which is our prime concern. We could not mention all the "experimental" operations for this complex condition because none has yet been shown to stand the test of time.

We wish Dr Glaser and his colleagues good fortune in their efforts to help patients with tricuspid atresia complicated by transposition and subaortic obstruction and look forward to reading about their long term survivors.

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Br Heart J 1988;59:146

Notices

British Cardiac Society

The Annual General Meeting for 1988 will take place in Belfast on 23 and 24 March 1988, and the closing date for receipt of abstracts will be 4 January 1988.

Advanced cardiology

The British Council is holding an Advanced Cardiology Course in Edinburgh on 12 to 22 April 1988. Further information from the Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA.

Echocardiography and Doppler in cardiac surgery

The 1st International Symposium on Echocardiography and Doppler in Cardiac Surgery will be held in Vienna on 25 to 27 April 1988. Inquiries to: Dr Werner Mohl, c/o Cosmos Convention Service, Kaerntner Ring 15, A-1015 Vienna, Austria.

Non-surgical intervention in coronary artery disease

The 5th Einthoven Meeting on Past and Present Cardiology—theme "Non-surgical intervention in coronary artery disease"—will be held in Leiden on 27 and 28 May, 1988. Inquiries to Professor A V G Bruschke, University Hospital, Department of Cardiology, PO Box 9600, 2300 RC Leiden, The Netherlands.

Hellenic Cardiological Society

The Xth Panhellenic Cardiological Congress will be held in Athens on 8 to 10 September 1988. Inquiries to Hellenic Cardiological Society, 17 Sissini Str, 115 28 Athens, Greece.

Br Heart J 1988;**59**:147–8

CHECKLIST

Please make a photocopy of this checklist, complete, and send with all manuscripts submitted for publication.

General

☐ Two complete sets of the manuscript (including 2 sets of figures) are submitted.

☐ The manuscript is typed double spaced throughout on one side only on 22 × 28 cm (8½ × 11") opaque white bond paper with 3 cm margins all around.

☐ The manuscript is arranged as follows: (1) title page, (2) summary, (3) text, (4) references (5) legends, (6) tables. Pages are numbered consecutively, beginning with the title page as page 1.

☐ The last name of the first author is typed at the top right corner of each page.

Title page

☐ The title and authors' names with symbols (* † ‡ etc) to indicate place of appointment are typed on the title page.

☐ No more than three authors' names should be given for case reports.

☐ The name and address of the institutions from which the work originated are included.

☐ The full name, exact *postal* address with postal code, and telephone number of the author to whom communications, proofs, and requests for reprints should be sent are typed at the bottom.

Summary

☐ A summary (excluding statistical analyses) is typed double spaced on a separate page.

☐ The summary is substantive rather than purely descriptive.

☐ Abbreviations other than standard units of measurement are not used.

Text

☐ Abbreviations or acronyms are always written out in full (for example, ECG, electrocardiogram; LVH, left ventricular hypertrophy; CAD, coronary artery disease, MI, myocardial infarction).

☐ Only units of measurement and mathematical formulas and calculations are abbreviated and they follow the form recommended in *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (*Br Heart J* 1984; **51:** 1–6).

☐ Appropriate headings and subheadings are provided.

☐ Every reference, figure, and table is cited in the text in numerical order. (Order of mention in text determines the number given to each.)

☐ Acknowledgments and details of support in the form of grants, equipment, or drugs are typed at the end of the text, before references.

References

☐ References are identified in the text by arabic numerals; no more than three references are cited for any one statement.

☐ References are typed double spaced on sheets separate from the text (*numbered consecutively in the order in which they are mentioned in the text*) in the Vancouver style.

☐ Journal references contain *inclusive* page numbers; book references contain *specific* page numbers.

☐ Citations of abstracts and letters should be indicated in parentheses.

☐ Personal communications, manuscripts in preparation, and other unpublished data are not cited in the reference list but are mentioned in the text in parentheses.

☐ Abbreviations of journals conform to those used in *Index Medicus,* US National Library of Medicine. The style and punctuation of the references follow the format illustrated in the following examples:

Journal: (list *all* authors if six or less; otherwise list first three and add *et al*; do not use full stops after authors' initials)

31 Balcon R, Brooks N, Layton C. Correlation of heart rate/ST slope and coronary angio-

graphic findings. *Br Heart J* 1984; **52:** 304–8.

Chapter in book:

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Book (personal author or authors): (all book references should have specific page numbers)

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Br Heart J 1988;**59**:149–50

Editorial

Regression of coronary atherosclerosis: is it possible?

JAMES SHEPHERD, CHRISTOPHER J PACKARD

From the Department of Biochemistry, Royal Infirmary, Glasgow

1984 was a good year. Contrary to orwellian predictions of doom it heralded a new era of confidence in the possibility of reducing the impact of coronary heart disease in the community. At a cost of $150 million, and with a one tailed *t* test significance of $p < 0{\cdot}05$, the Lipid Research Clinics Coronary Primary Prevention Trial (sponsored by the National Institutes of Health) produced convincing evidence that lowering plasma concentrations of cholesterol in symptom free hypercholesterolaemic men reduces the likelihood of their having a myocardial infarction.[1] This study highlighted the graded benefit to be gained from increasing the vigour of treatment to lower blood lipids and popularised the concept that a 1% fall in total plasma cholesterol should lead to a 2% reduction in coronary heart disease risk.[2] A rapid succession of additional reports[3-5] culminating in the eagerly awaited Helsinki Heart Study,[6] underscored the importance of cholesterol reduction in any programme designed to attack coronary disease.

The pharmaceutical industry has not been slow to appreciate the importance of these findings. New lipid lowering agents and old friends in fresh guise are being offered to the physician. This expansion widens choice, but also carries with it the need to establish the benefit/risk ratio of the regimen, which may be prescribed for the remainder of the patient's life. Ideally we would like to know whether all newly introduced lipid lowering agents are able to cut coronary morbidity and mortality, but the cost of such prospective studies is prohibitive. There is, therefore, a pressing need to identify a different, possibly softer, end point. Coronary angiography is the obvious candidate, even though it tests only one part of the overall pathophysiology of the disease. It allows us to assess the state of the lesion but cannot be used predictively to identify when or in whom we may expect to see an infarct. Nevertheless, this direct indicator of lesion progression or regression may provide a good measure of the efficacy of lipid lowering drugs.

How realistic is it to expect that human atherosclerotic lesions can be made to regress?

The pathologist, who sees these lesions every day, would probably take the view that the tissue damage and inflammatory response that characterise them are unlikely to respond to currently available regimens. In fact, the advanced atherosclerotic plaque with its fibrous cap, necrotic core, widespread calcification, and infiltrates of inflammatory cells appears to be a permanent, continuing feature of the patient's remaining years. In theory, however, all of these elements are amenable to mobilisation or even degradation.

Recent studies have shown that even the lipid core within the plaque[7] is continually turning over, albeit slowly, and may therefore (under appropriate conditions) be leached from the lesion. Certainly, studies in animal models have shown that it is possible to mobilise arterial wall cholesterol and induce regression if a satisfactory reduction in plasma cholesterol can be achieved.[8] Until recently most lipid lowering drugs could be expected to reduce cholesterol by no more than 25%, and clinical investigators had to be satisfied with lesion stasis rather than regression[3 9] as an acceptable end point of their arteriographically monitored intervention studies. Now, the availability of new, powerful lipid lowering agents may have made regression a more readily attainable objective. They also offer an improved prognosis for the increasing number of patients crippled by coronary artery disease for whom bypass grafting is viewed as the only alternative.

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The long term benefits of this procedure are limited because up to a third of the grafts will have become stenosed within a year of operation.[10] Fresh hope for these patients comes from the recently published Cholesterol Lowering Atherosclerosis Study (CLAS) in which 162 men who had had coronary bypass surgery were treated by a combination of diet, colestipol, and nicotinic acid in the expectation that their remaining coronary atherosclerotic lesions might be induced to regress.[5] This treatment lowered low density lipoprotein cholesterol by 43% (from 4·42 to 2·51 mmol/l) and raised the high density lipoprotein concentration by 37% (from 1·15 to 1·57 mmol/l), so that the ratio of total/high density lipoprotein cholesterol was reduced almost to the value at which regression is the rule rather than the exception in animal studies.[8]

An additional feature of the CLAS study was that benefit of treatment was evident across the whole range of plasma cholesterol values found at entry. Even patients who would be considered to have "normal" plasma cholesterol concentrations (as low as 4·8–6·2 mmol/l) benefited from cholesterol reduction. This finding accords with the results of the massive Multiple Risk Factor Intervention Trial, which showed that coronary risk was continuous across the population range for cholesterol concentration.[11]

What are the implications of these findings?

The arguments developed above have important implications for cardiologists and cardiac surgeons. The weight of evidence suggests that regression of coronary lesions is attainable, but only with vigorous and effective treatment to reduce blood lipids. In practice this means a reduction of at least 40% in low density lipoprotein cholesterol. At the moment this is only possible with combinations of drugs such as sequestrant resins coupled with nicotinic acid or clofibrate derivatives. The potential for the newly developed 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors is considerable because by inhibiting synthesis of cholesterol, particularly in the liver, they make it possible to achieve cholesterol reductions of up to 68%.[12 13]

The message for the cardiac surgeon is quite clear. Bypass grafting has an immediate impact on symptoms but does little for the prognosis of most patients unless the underlying causes of the disease are tackled. All patients who have had bypass grafts should share in the benefit that comes from treating the factors in their lifestyle that affect their coronary risk. Vigorous treatment to lower blood lipids is essential in these individuals.

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Acute complications of elective coronary angioplasty: a review of 500 consecutive procedures

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SUMMARY In 500 consecutive procedures of elective coronary angioplasty attempted at a centre with a primary success of 86%, one or more major acute complications occurred in 34 cases (6·8%). Twenty four patients (4·8%) sustained an acute myocardial infarction (in six this was despite emergency coronary artery bypass surgery) and two patients (0·4%) had emergency coronary bypass without myocardial infarction. Ventricular fibrillation was a complication without sequelae in five (1·0%) patients; one (0·2%) patient died because of refractory ventricular fibrillation and ensuing electromechanical dissociation. "Benign" coronary artery rupture occurred in one (0·2%) patient, and one (0·2%) patient had elective coronary surgery to retrieve the tip of a fractured guide wire after an otherwise successful angioplasty.

Despite a low mortality, coronary angioplasty is associated with major complications in about one of 14 procedures; the complication is usually acute myocardial infarction caused by occlusion of the vessel.

Since the introduction of percutaneous transluminal coronary angioplasty by Gruentzig in 1977[1] there has been considerable interest in the benefits and complications of this technique.[2 3] Reports of complications came from large series, but in many of these reports the results were influenced by the early use of non-steerable dilatation systems.[4-8] The first phase of the operators' learning curve[9] was included when smaller series were pooled.[7 8] Other very large series are based on the results of several operators working in a single large institution with a heavy case load.[10]

This paper analyses the major complications encountered in a series of 500 consecutive procedures of elective percutaneous transluminal coronary angioplasty with steerable dilatation systems. The procedures were performed by, or in cooperation with, one interventional cardiologist with considerable training and experience in percutaneous transluminal coronary angioplasty. Data from this study may be relevant to other centres where percutaneous transluminal coronary angioplasty is being initiated according to recently recommended standards.[11]

Patients and methods

Between July 1983 and January 1986, 500 consecutive procedures of elective percutaneous transluminal coronary angioplasty were attempted at our centre by, or under supervision of, a staff cardiologist with an extensive training in percutaneous transluminal coronary angioplasty. There were 430 men (86%) and 70 women (mean (SD) age 55 (9) years, range 23–76 years). In 110 cases (22%) the patient was in New York Heart Association class IV for angina.

A common strategy was followed in all procedures: no lesion on a vessel supplying collateral flow to another vessel was attempted until the latter had been revascularised, except when the amount of viable myocardium in the corresponding territory was presumed to be insignificant. Recanalisation of chronic occlusion in the presence of viable myocardium was attempted when the presumed duration of occlusion was <6 months. When patients with two or three vessel disease had stable angina they were considered as candidates for percutaneous transluminal coronary angioplasty if all the important lesions were suitable for dilatation and when they had

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unstable angina they were regarded as candidates if one critical lesion that was suitable for percutaneous transluminal coronary angioplasty could be clearly identified as being responsible for the symptoms and electrocardiographic signs of acute ischaemia.

All procedures were performed by the transfemoral route, with steerable dilatation systems (Schneider Shiley, Zurich, Switzerland). The details of the technique have been described elsewhere.[12] Intravenous heparin (10 000 IU) was given after the femoral sheath was in position and an additional 5000 IU was given an hour later if the procedure had not been completed by then. Intracoronary nifedipine (0·1 mg) and isosorbide dinitrate (0·2 mg) were given before dilatation and repeat doses were often given after balloon inflation. The femoral sheaths were usually removed in the ward 4–8 hours after the procedure, but they were sometimes left in place for up to 48 hours when the results were equivocal. Continuous intravenous infusions of isosorbide dinitrate and heparin were used and access for follow up coronary angiography or a repeat procedure was deemed necessary.

When there was acute occlusion of the dilated vessel in the catheterisation laboratory emergency recanalisation was attempted by repeat percutaneous transluminal coronary angioplasty, and if thrombus was present intracoronary streptokinase was also given. Intracoronary isosorbide dinitrate or nifedipine or both were given freely to counteract coronary spasm. When patients already in the ward developed signs or symptoms of acute ischaemia a follow up coronary arteriogram was obtained if the identity of the responsible vessel was uncertain, or if emergency recanalisation seemed feasible. Emergency coronary bypass surgery (within 12 hours) was performed when major signs and symptoms of acute ischaemia developed after the occlusion of an important vessel in which percutaneous recanalisation could not be attempted or had been unsuccessful.

All coronary stenoses were evaluated before and after percutaneous transluminal coronary angioplasty by visual estimation in all available projections by two independent angiographers and results were averaged. Intimal dissection was defined as the presence of an intimal flap with a double lumen contour or persistent staining of the vessel wall by contrast material. Acute occlusion of the dilated vessel was defined as an appreciable worsening in vessel patency with a severe impairment of distal progression of contrast. Primary success was defined as an improvement in the angiographic appearance of at least the ischaemia-related lesion, and of the transstenotic gradient whenever available, with no residual stenosis of >50%, in the absence of acute myocardial infarction or the need for emergency coronary surgery, and in the presence of a clinical improvement in angina of at least one class. Myocardial infarction was defined as an increase in plasma creatine kinase (>280 U/l) and an MB fraction of ⩾10% of total creatine kinase. Plasma creatine kinase concentrations were routinely assessed about eight hours after the procedure, and every six hours thereafter (if the initial findings were abnormal) until a peak was reached. Electrocardiograms were routinely recorded immediately after the procedure and the next morning. Tracings at discharge were obtained in patients with complications.

Data are expressed as mean (SD) values. We used Student's *t* test and the χ^2 test as appropriate; p values of <0·05 were regarded as significant.

Results

In 500 consecutive procedures 590 vessels were attempted. The Table shows the vessel distribution

Table *Distribution of vessels dilatated and frequency of acute coronary vascular events*

	Vessels					
	LAD	*RCA*	*Cx-Mg*	*Dg*	*BP*	*Total*
		Stenosis < 100%				
	240	119	109	26	9	503
Stenosis before PTCA (%)	82 (10)	84 (7)	82 (6)			
	NS		NS			
Acute vessel occlusion	10 (4·2%)	17 (14·3%)	3 (2·7%)			30 (6%)
	p < 0·02		p < 0·01			
		NS				
Acute side-branch occlusion	..	..	.	..	..	9 (1·8%)
		Stenosis = 100%				
	38	32	13	3	1	87
Acute side-branch occlusion	..	.	..	.	..	2 (2·3%)

BP, bypass graft, Dg, diagonal branch; Cx-Mg, circumflex coronary artery or marginal branch; LAD, left anterior descending coronary artery; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery.

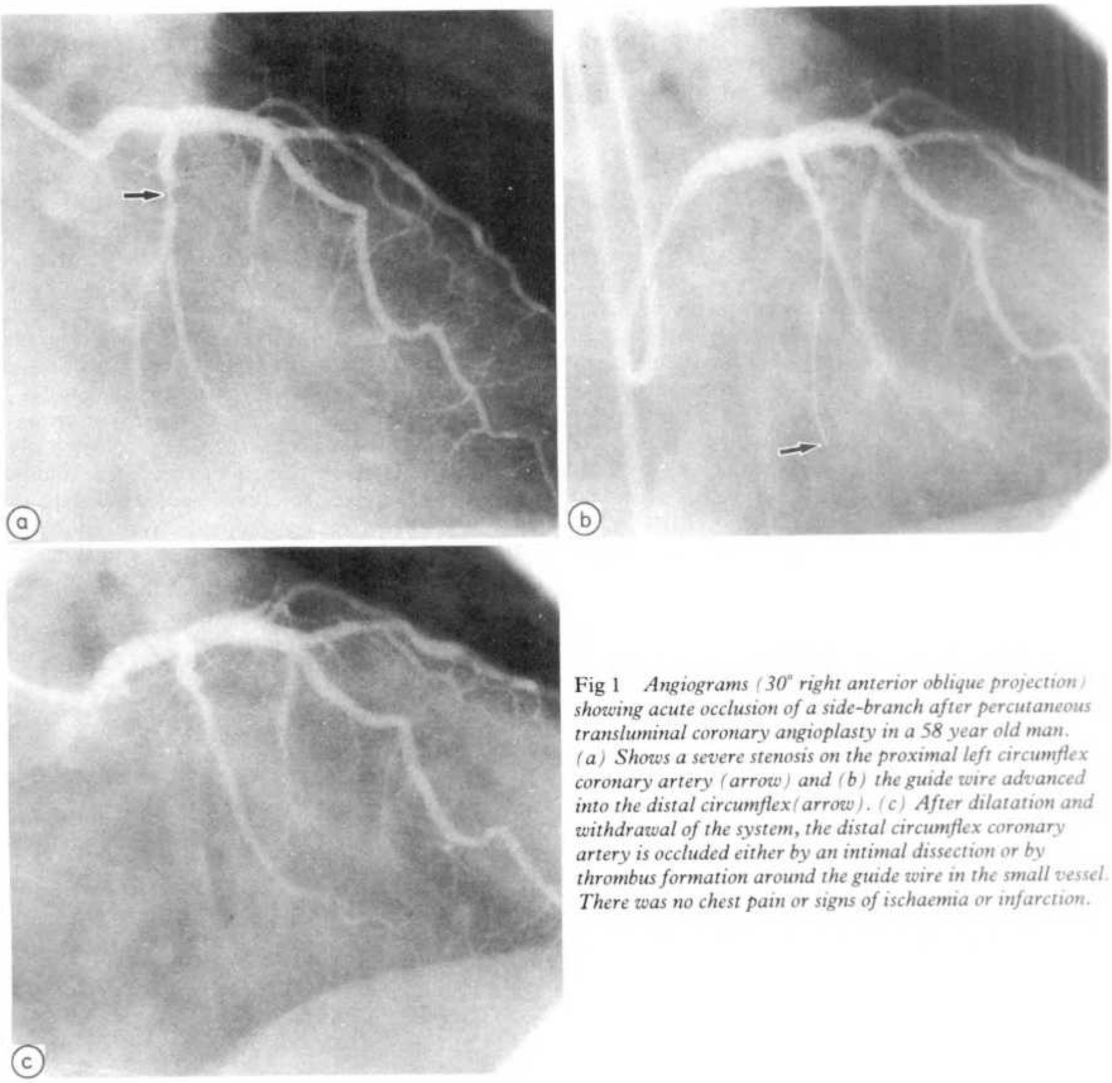

Fig 1 *Angiograms (30° right anterior oblique projection) showing acute occlusion of a side-branch after percutaneous transluminal coronary angioplasty in a 58 year old man. (a) Shows a severe stenosis on the proximal left circumflex coronary artery (arrow) and (b) the guide wire advanced into the distal circumflex (arrow). (c) After dilatation and withdrawal of the system, the distal circumflex coronary artery is occluded either by an intimal dissection or by thrombus formation around the guide wire in the small vessel. There was no chest pain or signs of ischaemia or infarction.*

and the frequency of occlusive complications. Two vessels were attempted in 80 cases and three vessels in five cases: multivessel percutaneous transluminal coronary angioplasty was attempted in 17% of cases. In 87 cases (17%) recanalisation of a chronic occlusion was attempted (in 27 patients as a part of a multiple vessel percutaneous transluminal coronary angioplasty and in 60 patients as an isolated procedure). Primary success was achieved in 429 (86%) cases. One or more of the major acute complications described below occurred in 34 (6·8%) cases.

Life-threatening arrhythmias and death—Six (1·2%) cases had ventricular fibrillation; in five cases during the procedure, possibly as a consequence of catheter wedging in the coronary ostium or of acute ischaemia of side-branches during catheter manipulation. It responded promptly to the re-establishment of flow, and to DC shock, and the procedure was otherwise uncomplicated, except in one case where the DC shock converted ventricular fibrillation into a supraventricular rhythm with no mechanical activity, and the patient could not be resuscitated. This was a 54 year old man with severe three vessel and bypass graft disease, poor ventricular function, and unstable angina after a repeat coronary bypass intervention. In one case ventricular fibrillation occurred about 30 minutes after the end of a successful procedure and responded promptly to DC shock. It was possibly caused by transient coronary spasm, which could not, however, be documented at follow up coronary angiography. Ventricular fibrillation was a complication in 3·4% of cases of chronic total coronary occlusion and 0·6% of cases with less severe lesions ($p < 0·02$).

Side-branch occlusion. In 11 cases (1·9% of vessels and 2·2% of patients) a side-branch (fig 1) became occluded during or immediately after percutaneous transluminal coronary angioplasty. Occlusion was as common during attempts on chronic occlusions as it was during attempts on stenosis (2·3% and 1·8% of cases, respectively). A policy of conservative management was followed in all cases. In two cases the presence of collaterals prevented the occurrence of myocardial infarction. In nine patients a rise in the activity of plasma creatine kinase indicated a myocardial infarction (mean peak 614 (328) IU/l, range 280–1200 IU/l, normal value <280 IU/l).

Occlusion of a dilated vessel. Acute occlusion occurred in 30 (6%) of 503 attempted stenoses (6·8% of 440 patients at risk). In 22 (73%) cases, it occurred in the catheterisation laboratory during or immediately after the procedure and in eight cases on the ward. In five of these eight it was sudden and unexpected (mean 6·2 hours from the end of the procedure (range 2–12 hours)); the other three cases had symptoms and signs of coronary occlusion 20, 24, and 48 hours after the procedure, within 1–3 hours of stopping intravenous heparin infusion. In 21 (70%) of 30 cases of vessel occlusion there was angiographic evidence of intimal dissection at the end of the procedure (fig 2). In three cases, occlusion occurred before balloon dilatation while the guide wire was being advanced, and it was probably caused by the plaque being raised. In only one case did angiography strongly suggest coronary spasm; however, there was a poor response to intracoronary vasodilators. Repeat percutaneous transluminal coronary angioplasty re-established vessel patency without further complications. Mean luminal diameter stenosis before percutaneous transluminal coronary angioplasty in vessels with acute occlusion

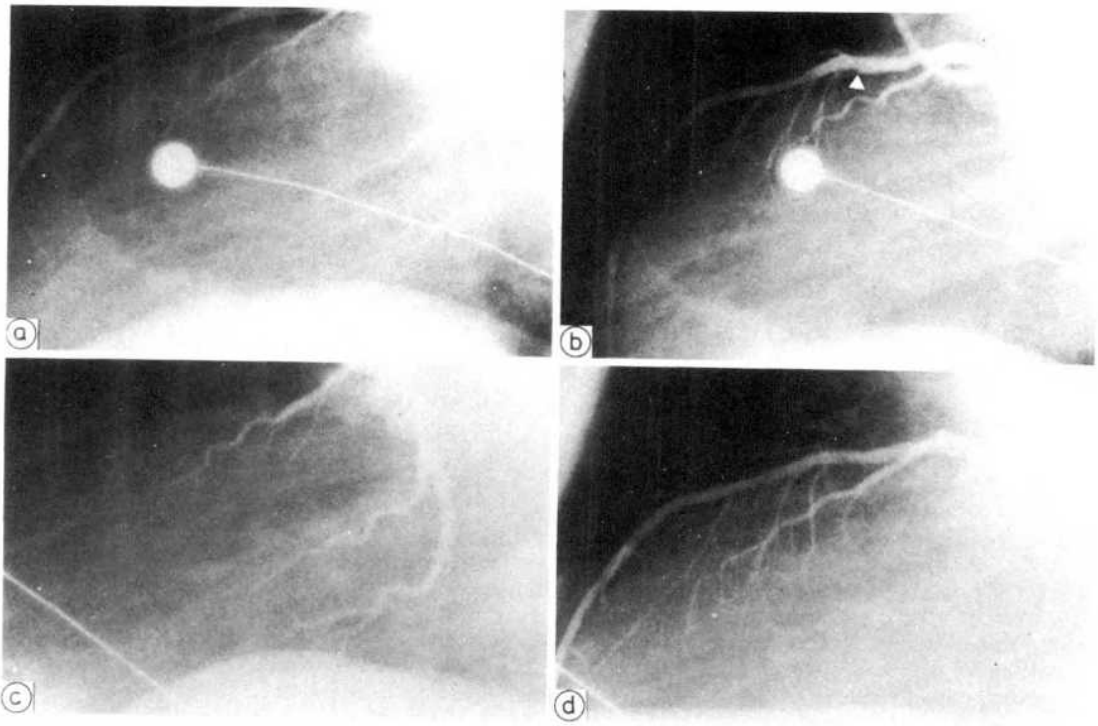

Fig 2 *Angiograms (90° left lateral projection) showing acute vessel occlusion after percutaneous transluminal coronary angioplasty in a 57 year old man. (a) Severe proximal stenosis of the left anterior descending coronary artery. (b) Good angiographic result after percutaneous transluminal coronary angioplasty, with a final transstenotic gradient of 15 mm Hg. Evidence of intimal dissection (arrowhead). (c) Follow up angiogram obtained seven hours later because of sudden chest pain with ST-segment elevation in anterior leads (acute vessel occlusion). (d) Good result of emergency balloon recanalisation.*

was 86 (6)% compared with 80 (10)% in vessels without this complication ($p < 0.05$). Acute occlusion was more common (table) after dilatation of the right coronary artery (14·3%) than the left anterior descending coronary artery (4·2%) ($p < 0.02$) and the circumflex coronary system (2·7%) ($p < 0.01$), with no significant difference between the last two arteries. The mean luminal diameter stenosis before percutaneous transluminal coronary angioplasty was not significantly different for the three vessels. The frequency of acute occlusion of a coronary vessel was not significantly different in men and in women (6·5% and 2·9%, respectively) or in patients with New York Heart Association class IV angina and with less severe angina (4·6% and 6·4%, respectively). The frequency of occlusion of a coronary vessel or side-branch was not significantly different in multivessel and in single-vessel percutaneous transluminal coronary angioplasty procedures (9·4% and 8% respectively). Emergency repeat percutaneous transluminal coronary angioplasty (figs 1 and 3) was attempted in 24 cases and in four of them an intracoronary infusion of streptokinase was also given to restore patency of the occluded vessel. Emergency repeat percutaneous transluminal coronary angioplasty was performed in 20 of 22 cases of occlusion in the catheterisation laboratory and in four of eight cases of delayed occlusion on the ward. Recanalisation was successful in eight (33%) patients, three of whom nevertheless sustained an acute myocardial infarction.

Emergency bypass surgery (fig 3) was performed in eight cases (1·6% of all procedures and 1 8% of patients at risk). In three patients it was not preceded by attempted recanalisation: one of these patients had an acute myocardial infarction. All 5 patients who had emergency coronary surgery after attempted percutaneous recanalisation had evidence of acute infarction. The mean time from coronary occlusion to cardiopulmonary bypass for the eight patients was 197 min (120–290 min). Six of them had enzyme evidence of acute infarction, with new Q waves in three. In four cases, two or more coronary arteries were grafted. One case was complicated by cardiopulmonary arrest, acute respiratory failure, and sepsis after operation. There was no hospital death among the patients with emergency bypass surgery.

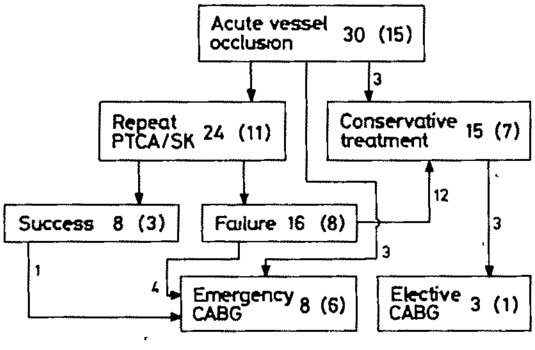

Fig 3 *Chart showing how acute vessel occlusion after percutaneous transluminal coronary angioplasty (PTCA) was treated. The total number of patients is indicated for each box and numbers crossing over are shown. Figures in parentheses indicate number of patients with evidence of acute myocardial infarction during hospital stay.*
SK, intracoronary streptokinase; CABG, coronary artery bypass grafting.

Conservative treatment was chosen for 15 patients with acute vessel occlusion without severe symptoms and signs of ischaemia because there was collateral flow and/or previous myocardial infarction in the area of the affected vessel. Seven (50%) of these patients subsequently had a myocardial infarction. Overall, myocardial infarction occurred during attempted percutaneous transluminal coronary angioplasty in 15 of 30 cases with acute vessel occlusion, or 3·4% of procedures at risk; the mean plasma creatine kinase peak was 946 (800) IU/l (range 285–3000 IU/l, median 760 IU/l). On the basis of purely biochemical evidence, the mean size of myocardial infarctions caused by occlusion of a side-branch was smaller than that caused by occlusion of a main vessel (614 (328) *vs* 946 (800) IU/l, $p < 0.05$). All patients with complications of occlusion of a main vessel or side-branch were discharged alive.

One patient had a benign coronary artery rupture[13] and another needed an operation to retrieve the tip of a fractured guide wire after an otherwise successful double-vessel percutaneous transluminal coronary angioplasty. It was performed one day later and it was uneventful.

There was no significant difference between the mean age of patients with and without complications (56 (10) and 55 (9) years respectively).

Discussion

Primary success in our series (86%) is similar to that in other recent reports[10 14] in which a lower percentage of multivessel procedures were performed.

Angioplasty of isolated chronic total coronary occlusions was performed in 12% of our series. Acute reocclusion of the recanalised vessel in this setting is usually uneventful.[15] Such procedures should, therefore, be excluded before calculating the frequency of major complications of procedures at risk.

The most frequent coronary vascular event in our patients after a dilatation attempt was acute occlusion of a previously patent coronary vessel. It occurred in 6·8% of procedures at risk in our series. Acute vessel occlusion rates of about 5% were reported by the National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty Registry[5] and the French cooperative study,[7] and of 8% by other groups.[8] Consistent with other reports,[16] about two thirds of acute occlusions occurred within three hours of the end of the procedure in our patients. Evidence of intimal dissection at the site of dilatation was reported in 19–29% of patients after percutaneous transluminal coronary angioplasty.[5,10] It was shown angiographically in most of the acute occlusions in our study, which accords with other reports.[10,16] Other factors, such as coronary spasm or thrombosis, may contribute to acute coronary occlusion after balloon dilatation, as shown in large studies[5] and in case reports.[17] The contribution of these factors, however, is uncertain and angiographic evidence is often not clear cut.[18,19] In our series, angiographic findings were strongly suggestive of coronary spasm in one case only. This may be because intracoronary nitrates and nifedipine were used freely. Thrombosis may have contributed to occlusion of vessels in the ward when the effect of heparin was declining. In three cases angiographic evidence of thrombosis prompted the administration of intracoronary streptokinase.

Women are reported to be at a higher risk of acute coronary vascular events[5,8] and major complications[10] after percutaneous transluminal coronary angioplasty. In our study evidence supporting this finding was inconclusive. Severe and unstable angina was also associated with a higher frequency of acute coronary vascular events in the patients of the National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty Registry[5] but not in ours. Our finding is consistent with that of other reports.[10] In our series more severe lesions were more liable to acute occlusion after percutaneous transluminal coronary angioplasty. This accords with evidence from the United States registry[5] but not with other reports.[10] In our series lesions of the right coronary artery were more liable to acute occlusion than lesions in other vessels, despite similar degrees of luminal stenosis before percutaneous transluminal coronary angioplasty. This was not reported in other series.[8] Both univariate and multivariate analysis of data from the United States registry showed that intimal dissection was significantly more common after percutaneous transluminal coronary angioplasty of the right coronary artery. Percutaneous transluminal coronary angioplasty of the right coronary artery, however, was neither a predictor of acute coronary occlusion[5] nor of overall non-fatal complications.[4]

The frequency of acute vessel occlusion in our patients who had a multivessel procedure was not significantly higher than in those who had single-vessel lesions. In about a third of our patients having a multivessel procedure recanalisation of a chronic total occlusion was attempted.

The treatment of acute coronary occlusion after an angioplasty attempt has probably changed in several centres over the past ten years and remains controversial. In earlier series[7,14,20–22] emergency coronary bypass surgery was performed in 4·8–13% of patients in whom percutaneous transluminal coronary angioplasty was attempted and the frequency in the National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty Registry was 6·6%.[23] More recent reports show a decline in emergency coronary surgery to 2%, along with an increase in the frequency of acute myocardial infarction without emergency surgery.[10] Insertion of an intra-aortic balloon for counterpulsation before emergency surgery has also been recommended for patients with severe ischaemia.[24] The choice of treatment for acute vessel occlusion after percutaneous transluminal coronary angioplasty depends on several factors. Where percutaneous transluminal coronary angioplasty is performed between scheduled bypass operations an operating room may not be available if emergency surgery is needed some time after the end of an initially successful percutaneous transluminal coronary angioplasty procedure.[20] About 40–60%[10,21,23–25] of patients who have emergency coronary surgery after percutaneous transluminal coronary angioplasty have evidence of myocardial infarction, despite prompt operation, and mortality ranges from 0–6·4%.[10,21–23,25] Emergency repeat percutaneous transluminal coronary angioplasty or intracoronary streptokinase or both have been advocated for treatment of acute occlusions after percutaneous transluminal coronary angioplasty.[15] About a third of patients undergoing emergency recanalisation attempts and all patients requiring subsequent emergency coronary surgery showed evidence of a new myocardial infarction.[15] Vessel recanalisation was attempted in most of our patients, and emergency coronary surgery was the first choice in only three cases. Whatever the first and subsequent treatments, half of our cases with acute vessel occlusion had evidence of myocardial infarction. Side-branch occlusion, caused by either a snowplough effect at the site of balloon inflation or by intimal injury or thrombosis by the guide wire (fig 1), was seen in about 2% of our patients, which is similar to previous reports.[10,26] Most cases had enzyme evidence of acute infarction. Although the specificity of the increases in plasma creatine kinase as a marker of myocardial necrosis after transient coronary occlusions has recently been questioned,[27,28] we used it for definition of myocardial infarction. The overall frequency of infarction in our series was 4·8% and this compares favourably with that in other series,[5 7] but it is higher than the 2·6% reported by the Emory University group which used a new Q wave as the criterion for diagnosis.[10]

In a large series ventricular fibrillation occurred in 1·5% to 2·9% of patients during percutaneous transluminal coronary angioplasty[6 10]; it is usually responsive to DC shock and recovery is uneventful—it is not usually regarded as a major complication. It occurred in 1·2% of our patients. In patients who have percutaneous transluminal coronary angioplasty for chronic total coronary occlusion ventricular fibrillation is more common because vigorous and persistent attempts on the occlusions cause temporary compromise of adjacent side branches and predispose the heart to electrical instability. Ventricular fibrillation was seen in the only patient in our series who died; however, the cause of death was ischaemic left heart failure. Our mortality rate (0·2%) is within the reported range of 0·1[10] to 1·3%.[8]

Elective percutaneous transluminal coronary angioplasty performed by experienced operators with modern steerable dilatation systems has a high primary success rate and a reasonably low mortality rate. Complications, usually myocardial infarction caused by acute vessel occlusion, occur in about one out of 14 procedures. Efforts should be directed to improving the treatment of acute vessel occlusion to prevent or limit myocardial necrosis.

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Haemodynamic observations during percutaneous transluminal coronary angioplasty in the presence of synchronised diastolic coronary sinus retroperfusion

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SUMMARY Animal studies have demonstrated that synchronised coronary sinus retroperfusion with arterial blood can provide effective perfusion of ischaemic myocardium. Preliminary clinical studies have shown that the technique can also be used with safety in human beings, and in the present study its effectiveness was assessed in three patients undergoing repeated coronary artery occlusions during percutaneous transluminal coronary angioplasty. Arterial blood was removed via an 8F catheter positioned in the femoral artery and delivered by a retroperfusion pumping system to a 7F retroperfusion balloon catheter positioned in the anterior cardiac vein. Ischaemia-related indices were monitored both before and during coronary sinus retroperfusion. These indices included high fidelity left ventricular pressure recordings and pressure derived indices (including velocities of isovolumic contraction and relaxation), as well as electrocardiographic changes and symptoms. Analysis of these variables showed that the ischaemic changes induced during coronary artery occlusion were not prevented by this type of coronary sinus retroperfusion. There was no major complication in any of the patients.

It may be that adaptation of the technique or the use of alternative end points will establish a benefit, but further modifications of the delivery system are necessary for effective clinical use.

The effective preservation of acutely ischaemic myocardium remains an elusive goal. Coronary sinus retroperfusion has been put forward as a practical technique for providing temporary support of jeopardised myocardium. The concept was originally tested in the clinical setting by Beck *et al* in the 1940s with disappointing results.[1] They used an aorta-to-coronary-sinus anastomosis with an artificially increased coronary sinus outflow resistance to shunt a proportion of the blood retrogradely. The increase in venous pressure, however, led to myocardial engorgement and eventual myocardial failure. In 1976 Meerbaum *et al*[2] introduced a synchronised delivery system that limited the delivery of arterial blood to the coronary sinus to diastole, thereby overcoming some of the original complications associated with the continuous increase in pressure in the coronary venous system. This technique was effective and safe in animal studies,[3] and improved myocardial salvage, myocardial perfusion, and indices related to ischaemia.[4-6] Although there is broad agreement on the safety of the procedure not all of the animal studies showed an improvement in myocardial perfusion.[7 8]

Clinical studies confirmed the safety of the procedure in human beings, and suggested that it may be useful in unstable angina and during percutaneous transluminal coronary angioplasty.[9 10] Recently Gore *et al* reported the experience of retroperfusion in five patients with acute ischaemia.[11] The procedure had no adverse effects and despite clinically encouraging results there was little objective evidence to support its effectiveness. We therefore conducted a pilot study in three patients to determine whether synchronised coronary sinus retroperfusion prevented transient loss of myocardial function, as assessed by central haemodynamic indices, during repeated occlusion of the coronary artery in percutaneous transluminal coronary angioplasty.

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Patients and methods

PATIENT SELECTION

We studied three patients who had easily provoked angina, a lesion of the proximal left anterior descending artery with a large area of potentially ischaemic myocardium, normal left ventricular anterior wall motion, and no angiographically demonstrable collateral supply to the potentially ischaemic area.

RETROPERFUSION SYSTEM

Oxygenated blood was delivered by a size 7 Fr single lumen, Nycore, retroperfusion catheter (USCI Division of Bard Inc. Billerica, MA, USA), 90 cm in length, and with a lumen diameter of 0·56 mm. This catheter consists of a balloon (maximal inflation diameter 10 mm) positioned close to the tip of the catheter that communicates with the central lumen of the catheter via a number of small holes. Thus when blood is pumped through the catheter, the increase in intraluminal pressure producing the flow through the catheter also causes the balloon to inflate, which in turn leads to occlusion of the coronary sinus lumen, thereby directing the delivered blood retrogradely (fig 1a). When flow ceases during systole, intraluminal pressure falls, the balloon deflates, and normal forward coronary sinus flow is resumed.

The tip of the catheter was positioned in the great cardiac vein, under fluoroscopic control with the aid of a 0·018 inch (Advanced Catheter Systems) high torque guide wire, and the position was verified by injection of contrast. Arterial blood was delivered to the catheter via a USCI synchronised retroperfusion system, model EC-I. Blood was removed with a special multihole catheter (8F, 40 cm (USCI)) introduced to the distal aorta via the femoral artery. There were three parts to the retroperfusion system: (*a*) a linear, constant force pump with a variable stroke volume; (*b*) a Hewlett Packard 7834 monitor to display selective electrocardiographic signals as well as perfusion and aortic pressures; (*c*) a pump control device that allowed the onset and duration of the pump stroke to be adjusted in relation to the triggering R wave. In addition, it allowed the volume of blood delivered per minute to be controlled independently of the heart rate.

HAEMODYNAMIC AND ELECTROCARDIOGRAPHIC MONITORING

Left ventricular pressure was measured by a Millar micromanometer catheter and digitised at 250 samples per second. A beat to beat computer program was used to analyse, display, and store the pressure signals for off line analysis. Peak left ventricular pressure, left ventricular end diastolic pressure, peak negative dP/dt, peak positive dP/dt, and the relation between dP/dt/pressure and pressure linearly extrapolated to pressure 0 (Vmax) (where Vmax is the maximal velocity) were computed for each measured beat. Tau$_1$, the time constant for the first 40 ms, taken from the bi-exponential model of the isovolumic relaxation period was also recorded. The definition of the pressure derived indices and their method of determination have been described elsewhere.[12-14]

Electrocardiograms from leads I, II, and V3 were recorded throughout the procedure and in addition an intracoronary electrocardiogram was recorded from the intraluminal balloon guide wire in one of the patients. The ST changes are expressed in mV and were recorded from the lead showing the maximal change in ST segment during occlusions, measured from the isoelectric line (P-Q interval) 0·08 seconds after the J point.

PROTOCOL

The protocol was approved by the ethics committee of the Thoraxcenter. The data were collected according to the guidelines of the Food and Drugs Administration of the United States and the procedures were performed with the technical assistance of representatives from the industry. Patients gave their informed consent to the study.

A pacing wire was positioned in the right atrium, and coronary angiography and left ventriculography were performed. The catheter for monitoring pressure was then positioned in the left ventricle and the retroperfusion catheter was inserted into the coronary sinus. The catheter for dilating the coronary artery was then introduced and the lesion was crossed. Two control dilatations were performed with haemodynamic monitoring before retroperfusion was started. This was started at an initial measured flow rate of 50 ml/min, increasing by 20 ml/min, up to 150 ml/min. Retroperfusion was then continued for 20 minutes. The extent of retroperfusion was assessed visually by direct hand injection of contrast (fig 1b). Two further investigational balloon dilatations were then performed.

Case reports

Patient 1—A 67 year old woman was admitted with chest pain at rest, which continued despite administration of intravenous isosorbide dinitrate. Coronary angiography showed an isolated severe proximal stenosis in the left anterior descending artery and she was therefore transferred to the Thoraxcenter for an immediate angioplasty. The retroperfusion catheter was satisfactorily positioned via the right femoral vein. Four balloon dilatations were performed at 10 atmospheres each—two before retroperfusion and

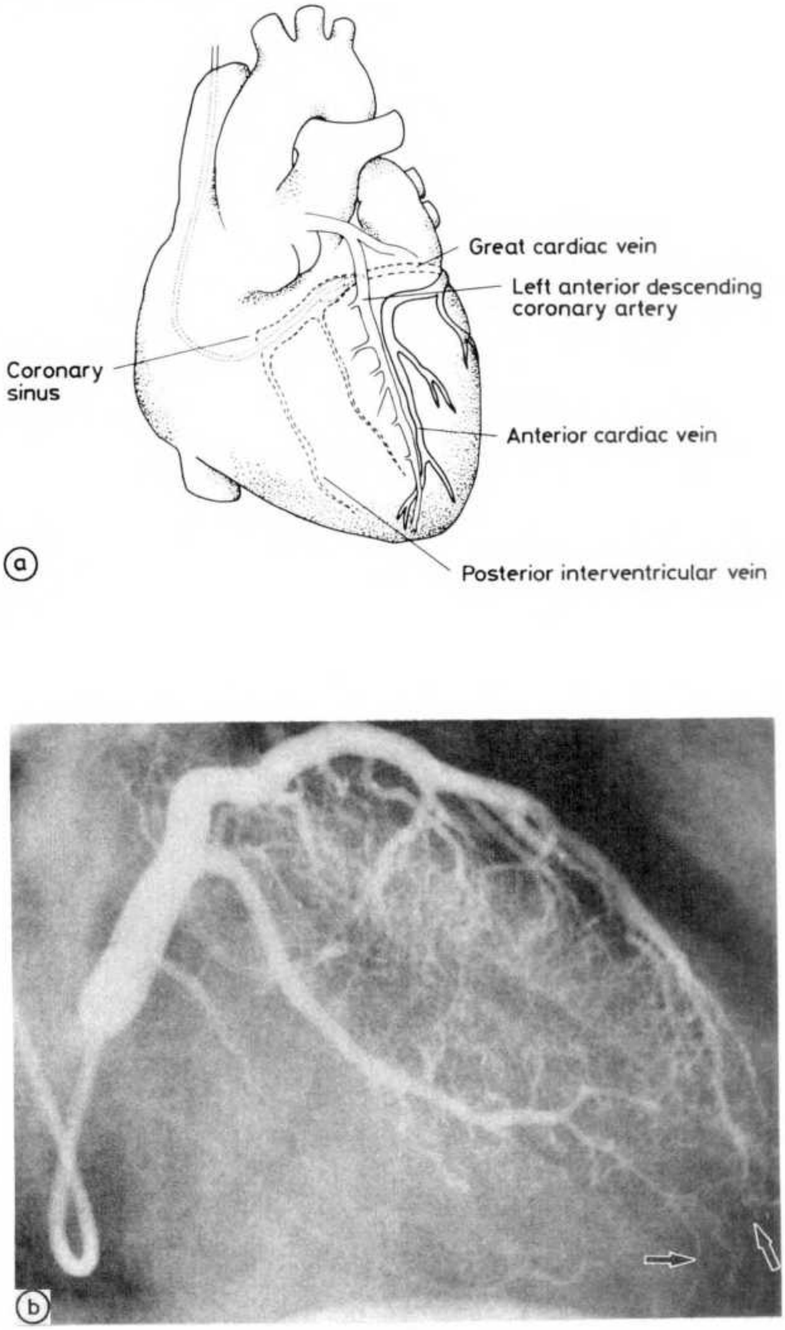
Great cardiac vein
Left anterior descending coronary artery
Coronary sinus
Anterior cardiac vein
Posterior interventricular vein
ⓐ
ⓑ

Fig 1 *(a) Diagram showing the retroperfusion catheter positioned in the great cardiac vein. (b) Single frame angiogram showing the retroperfusion catheter positioned in the great cardiac vein. The anterior cardiac vein is clearly delineated by hand injection of contrast. This produces a myocardial blush and shows the venous to venous collateral circulation (arrows).*

Table *Time(s) to ST change (mV) inflation and time to normalisation after deflation in patient 1*

	Occlusion			
	Baseline 1	*Baseline 2*	*SRP 1*	*SRP 2*
Time to:				
0·2 mV	10	15	20	18
0·4 mV	30	35	26	24
Normalisation (after deflation)	40	30	45	20

Baseline, before retroperfusion; SRP, during retroperfusion.

two afterwards. The duration of inflations ranged from 45 to 52 seconds. The stenosis of the left anterior descending artery was successfully dilated to a <50% diameter stenosis. The table shows the time to 0·2 mV and 0·4 mV ST changes during the occlusions. The measured indices of left ventricular peak systolic pressure, left ventricular end diastolic pressure, positive dP/dt, negative dP/dt, Vmax, and Tau$_p$, changed progressively during occlusion, in keeping with induced myocardial ischaemia. Figure 2 shows the electrocardiogram, left ventricular pressure, and retroperfusion flow recordings at the end of each occlusion compared with the baseline recordings. At the end of each occlusion there was 0·4 mV of ST elevation; there was considerable variability in the time taken for the changes to occur and resolve (table 1).

During each of the four occlusions there were ischaemia-induced changes in the pressure derived indices, with a more pronounced change in Vmax, Tau$_p$, and +dP/dt during the two occlusions performed with retroperfusion.

Patient 2—A 63 year old man was readmitted with chest pain at rest after a small anterior non-Q wave myocardial infarction. The pain was associated with anterior ST depression and T wave inversion. Coronary angiography showed an occluded right coronary artery and a severe proximal stenosis in the left anterior descending artery; it was therefore decided to proceed to coronary angioplasty. At angioplasty two 54 second inflations were performed before retroperfusion and one 174 second and one 54 second inflation were performed during retroperfusion. The maximal inflation pressure was 10 atmospheres. There was ST depression of 0·1 mV at the end of the first inflation, but not during the second inflation. The first inflation with retroperfusion was increased to 174 seconds, with the patient complaining of mild pain shortly after 30 seconds. There was no progression to severe chest pain during the procedure and only slow progression in ST change—0·1 mV at 70 s and 0·2 mV at 140 seconds.

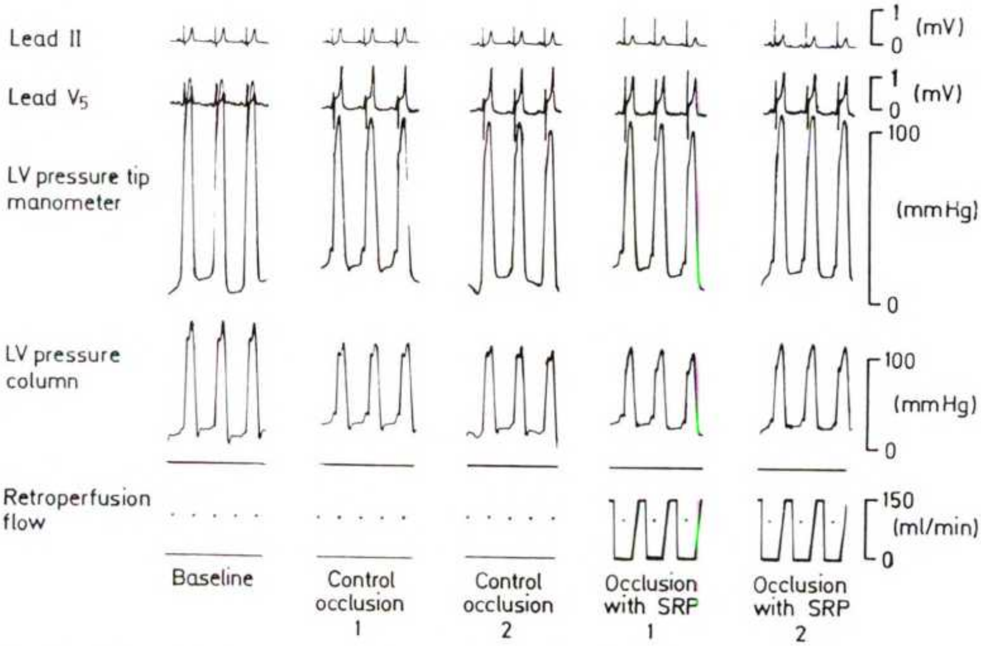

Fig 2 *Left ventricular pressure and surface electrocardiograms in patient 1 before the first occlusion, at the end of the two controlled occlusions, and at the end of the two occlusions with synchronised retroperfusion (SRP). The retroperfusion flow tracing (b) shows the magnitude of the flow and the timing in relation to the cardiac cycle. The ST changes in lead V5 and the changes in left ventricular pressure were similar for the four occlusions.*

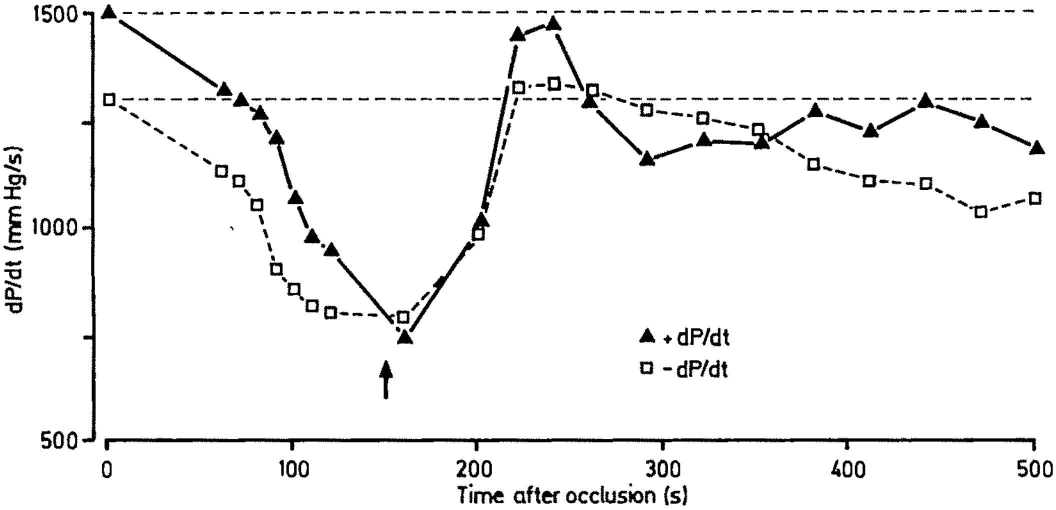

Fig 3 *Values of positive dP/dt and negative dP/dt during a 174 second occlusion in patient 2. The arrow shows the point of balloon deflation. Although some overshoot is seen in dP/dt, at 500 s both values remain below the starting value, suggesting some persisting depression of myocardial function.*

These changes resolved within 30 seconds of deflation. Figure 3 shows changes in + dP/dt and − dP/dt. Again the expected ischaemia-induced changes are clearly present. Although there was an "overshoot" in the + dP/dt on reperfusion, the change is not as pronounced as that seen during the shorter occlusions in patient 3 (fig 5b). In addition, the post-occlusion recordings (at 500 s) showed that all the pressure derived indices were lower than the baseline values, suggesting delayed recovery of the ischaemic myocardium.

Patient 3—A 64 year old man developed pain on minimal exertion and at rest when provoked by emotional or cold stimuli. Coronary angiography showed a single severe stenosis in the proximal left anterior descending coronary artery, and it was therefore decided to proceed to angioplasty. An initial inflation of 56 seconds produced no symptoms and therefore the inflation time was increased to 115 seconds without retroperfusion followed by two inflations with retroperfusion of 123 seconds and 116 seconds. All dilatations were performed at a maximal inflation pressure of 12 atmospheres. The left anterior descending lesion was successfully dilated without complications. The severity of the chest pain was categorised by the patient as mild, moderate, or severe on an analogue scale. Figure 4 shows the analogue scores and the degree of ST change during and immediately after balloon inflations. During all three occlusions there was a gradual decrease in left ventricular peak systolic pressure and an increase in end diastolic pressure, with no difference between

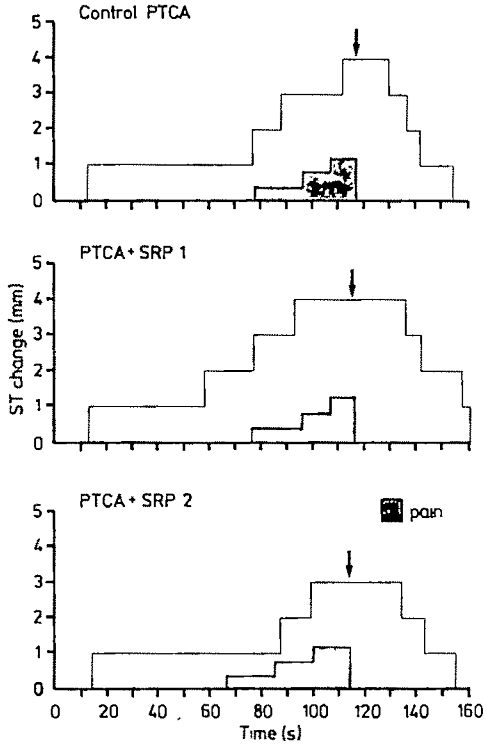

Fig 4 *Time to given ST change and degree of chest pain during three occlusions in patient 3, one without and two with synchronised retroperfusion (SRP). The three steps on the pain scale correspond to mild, moderate, and severe chest pain respectively.*

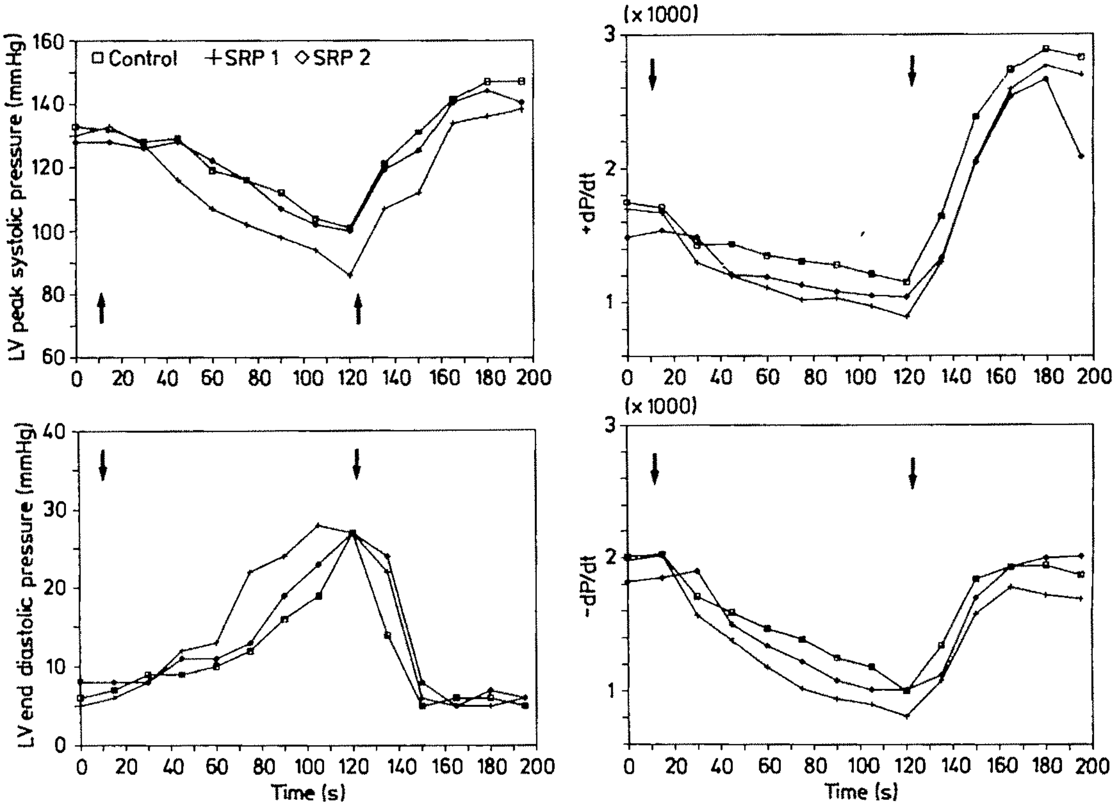

Fig 5 *(a) Left ventricular peak systolic pressure and end diastolic pressure during one controlled occlusion and two with synchronised retroperfusion (SRP) in patient 3. The arrows show the onset of balloon inflation and deflation. There is essentially no difference between the occlusions with retroperfusion and the one without. (b) Changes in + dP/dt and − dP/dt for the same three occlusions, showing a similar pattern to that for left ventricular peak systolic pressure and end diastolic pressure.*

the individual inflations (fig 5a). Similarly there was a reduction in Vmax and dP/dt and increase in Tau$_1$. There was a pronounced "overshoot" in positive dP/dt on deflation, before baseline values were restored. The changes in these variables all followed the same course during all the balloon inflations; retroperfusion did not produce any significant changes.

Discussion

FEASIBILITY AND SAFETY

Animal studies demonstrated that coronary sinus retroperfusion does not significantly damage the coronary sinus, the myocardium, or red blood cells.[2-4] This was confirmed in a limited number of patients in whom the procedure was performed.[9-11] Although, with prolonged retroperfusion there does seem to be loss of the coronary sinus epithelium, which may lead to the formation of a fine layer of thrombus and even small areas of haemorrhage adjacent to the sinus, this is not of any apparent clinical importance. In our study we had no information on the state of the coronary sinus epithelium, but no thrombus formation was identified by contrast injection of the sinus or by direct inspection of the catheter after removal. Furthermore, the lack of change of the haemodynamic variables during the control period of retroperfusion suggests that there was no adverse effect on myocardial function during normal anterograde flow, which accords with other reports.[10]

In all three patients the positioning of the catheter in the coronary sinus was a relatively simple procedure. In two patients a 0·018 inch high torque floppy guide wire was used to avoid entering the origin of the obtuse marginal vein. We found that once venous access was obtained the catheter could be positioned quickly so that when imaging is available it should be possible to set up the system and start retroperfusion within 15 minutes.

METHOD OF ASSESSMENT

There is no consensus about the most appropriate method of assessing improvement in myocardial perfusion and function during retroperfusion. Methods which have been used to demonstrate an improvement with retroperfusion in animals include the measurement of cardiac output, electrocardiographic change, regional and global left ventricular function by echocardiography, and postmortem assessment of myocardial ischaemia by intravascular indicators.

We chose to assess the effect of synchronised retroperfusion on myocardial ischaemia during angioplasty in three ways: (*a*) by evaluating the severity of chest pain and the length of artery occlusion before pain; (*b*) by monitoring the surface and in one case the intracoronary electrocardiogram; (*c*) by monitoring the left ventricular pressure and the pressure derived indices.

The assessment by the assessor and patient of chest pain in a stressed patient during an interventional procedure in which an experimental device is used is to some extent subjective. The use of an analogue scale may help to reduce this, but we believe that such an assessment will remain crude and will only be relevant when there are large changes.

ST change is widely used as an index of ischaemia although the variability of this measurement in the context of repeated coronary occlusion with intracoronary injections has not been well validated. Intracoronary electrocardiographic recordings taken from the balloon guide wire which overlies the area of ischaemic myocardium provides a more reliable measurement,[15] although there may still be some variability when there are sequential artery occlusions, where alterations in the resting membrane potential may give a false impression of ST change.[16] Perhaps the most reliable forms of measurement, particularly in assessing myocardial function, are left ventricular pressure and pressure derived indices. Serruys *et al* showed that measured changes correlate well with changes in regional and global left ventricular function and provide a reliable index for comparison during repeated episodes of ischaemia.[14]

EFFECTIVENESS OF PROCEDURE

An analysis of the individual's angina threshold and the documented ST change during coronary artery occlusion failed to show any consistent change during retroperfusion. Similarly, the change in left ventricular pressure and pressure-derived indices showed the predicted ischaemia-induced changes with no reversal during retroperfusion. Although there was a certain amount of variability in the time to chest pain and any given ST change the pressure-derived indices were more consistent, suggesting that this is a more reliable method of assessment (figs 4 and 5). Several animal studies showed that retroperfusion can be effective in improving myocardial ischaemia and reducing infarct size. In our study we failed to show any convincing benefit of retroperfusion during acute myocardial ischaemia. There are several reasons why there might be a discrepancy between animal and human studies, and among these must be the suitability of the given animal model. The results from canine studies have generally been more favourable, than those in pigs.[8 9] The capacitance and compliance of the human coronary sinus system is not known and it may be that this quantity of injected blood is insufficient to create the venocapillary gradient necessary to provide effective retroperfusion. The resting flow in the great cardiac vein varies from 40 to 99 ml/min at rest.[14] Animal studies have shown that myocardial function is reduced if the resting flow falls by 20%, although some benefit in terms of myocardial salvage may be retained even when flow rates are reduced by as much as 70%.[17 18] Even if only a proportion of a retrograde flow rate of 160 ml/min reaches the myocardium we might expect some improvement in function. Because the flow is limited to diastole, however, a large amount of the delivered blood is "washed out" before it reaches the capillary bed.

In our animal studies (unpublished data) we achieved effective retroperfusion in some cases with high flow rates and high coronary venous pressures by selective positioning of the catheter. In the present study we confirmed the position of the retroperfusion catheter in the great cardiac vein throughout the procedure in all three patients and demonstrated retrograde flow. Figure 2 shows a hand injection of 10 ml of contrast (not synchronised) producing clear visualisation of the anterior cardiac vein, with blushing of the myocardium, particularly in the septal area. The addition of contrast to the retroperfused blood during the procedure, however, suggested that synchronised delivery was much less effective at producing a myocardial blush, and it may be that higher flow rates will be necessary to achieve this. One of the very important considerations of using higher flow rates is the ability of the venous system to drain the increased volume of blood. In this report the comparatively slow deflation of the autoinflatable balloon is a serious limitation, and is one of the areas that need further development.

We feel that we performed appropriate monitoring to detect any improvement in the ischaemic state of the myocardium. The ischaemic response to repeated occlusion of the coronary artery may be variable; in particular the response may become blunted with repeated occlusions. By performing the occlusions with retroperfusion after the control occlusions, any improvement in the ischaemic response due to an improvement in anterograde flow may have been falsely attributed to the retroperfusion. Left ventricular function as assessed by our haemodynamic measurements, however, showed no improvement during occlusions with retroperfusion in any of our patients. Improvement in ischaemia may not be the only potential benefit of retroperfusion. Mohl *et al* have developed the concept of pressure-controlled intermittent coronary sinus occlusion,[19 20] in which the coronary sinus is occluded cyclically until a predetermined pressure is reached. Using the technique they have shown that toxic metabolites are washed out and this may be important in reducing the extent of infarction, particularly if subsequent reperfusion takes place. It is possible that this feature may also be a benefit of retroperfusion during transient ischaemia,[21] but the limitations of our model prevented us from assessing this.

FUTURE APPLICATIONS

The use of coronary sinus retroperfusion has been proposed in several clinical settings including myocardial infarction and unstable angina, retroperfusion of thrombolytic and antiarrhythmic drugs, and for cardioplegia. It is doubtful whether the procedure will become widely used in myocardial infarction and unstable angina because more effective forms of treatment with greater potential are becoming available. Of the other medical proposals, the delivery of thrombolytic and antiarrhythmic agents are unlikely to be substantially more effective than intravenous administration and the additional time and expense of retroperfusion may not be justified.

If retroperfusion can be shown to be effective, however, it could become a valuable aid to percutaneous transluminal coronary angioplasty. It would permit longer occlusions in general and would mean that more critical lesions such as those of the left main stem could be dilated with reduced risk of myocardial damage. It could also be useful in salvaging myocardium in those procedures in which a total occlusion occurs, by providing effective perfusion of the ischaemic area while the patient is prepared for bypass surgery.

We feel the weight of our current data precluded the use of this technique in additional patients. We have, however, been able to identify potential modifications which should substantially improve the current delivery system. It remains to be seen whether improved techniques of anterograde perfusion will make retroperfusion obsolete, but any future clinical trial must be conducted in a controlled manner and its conclusions must be based on reliable and reproducable indices of myocardial ischaemia.

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Laser recanalisation of coronary arteries by metal-capped optical fibres: early clinical experience in patients with stable angina pectoris

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SUMMARY The delivery of laser energy to the coronary circulation by bare optical fibres may cause perforation of the vessel. Experimental studies have shown that this complication can be avoided if the optical fibre is fitted with a metal cap to prevent the potentially dangerous forward projection of the laser beam. This study was performed to assess the feasibility and short term effects of percutaneous coronary laser recanalisation with these modified fibres. Recanalisation of a severe stenosis of the left anterior descending artery was attempted in six patients who were referred for coronary artery bypass grafting. Although the percutaneous technique was used, the laser procedure was performed during coronary bypass surgery before the start of cardiopulmonary bypass to minimise the effects of potential complications. A 1·5 mm diameter metal-capped fibre coupled to an argon laser was advanced percutaneously over a guide wire positioned across the stenosis. In the first patient the delivery of 152 J resulted in the gradual passage of the fibre through a 3 cm long stenosis. Repeat angiography showed a reduction in the severity of the stenosis. In the second patient the delivery of 112 J failed to allow fibre advancement; a further 80 J pulse caused perforation which was repaired. In the remaining four patients the delivery of laser energy in the attempt to traverse the stenosis was limited to less than 90 J. In two of the four patients the severity of stenosis was reduced. No further complications were seen.

Percutaneous coronary laser recanalisation with metal-capped optical fibres is feasible but improvements of currently available technology are needed to increase the primary success rate.

Experimental and clinical studies have shown that laser energy transported by optical fibres can recanalise atherosclerotic arteries.[1-3] Dissection, distal embolisation, thrombosis, and aneurysm formation are uncommon complications.[4-6] Laser recanalisation may be successful in arteries in which occlusion prevents the passage of a balloon catheter.[7] Furthermore, laser technology can remove the atherosclerotic plaque rather than remodel it [8-10]; and this could result in a lower restenosis rate than that seen after balloon angioplasty. Despite these theoretical advantages, use of this new technique in the coronary circulation has been hampered by the problem of arterial perforation—mainly caused by the difficulty of controlling the direction of the laser beam in tortuous arteries within the beating heart.[11 12]

Several modifications of the technique described in early experiments have been proposed to reduce the risk of perforation. These include use of pulsed lasers to achieve tissue ablation without thermal damage,[13-15] improvement of the guiding system by means of angioscopy or laser-induced fluorescence detection,[16-18] development of less traumatic delivery systems to avoid mechanical perforation,[19 20] and selective enhancement of laser energy absorption by the atherosclerotic plaque.[21-23]

Another approach is to prevent the potentially dangerous forward projection of the laser beam by crimping a metal cap on to the tip of the optical fibre. Experimental and clinical studies have shown that

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the heat generated by the interaction of laser energy with the metal cap is sufficient to recanalise occluded peripheral arteries by vaporisation of the atherosclerotic plaque.[24-27] We have previously demonstrated in live dogs that the intracoronary delivery of laser energy through metal-capped fibres allows a precisely targeted intimal vaporisation without perforation.[28] Based on these results we have assessed the feasibility of performing percutaneous coronary laser recanalisation in patients with stable angina pectoris by means of metal-capped optical fibres. The fibres we used in the coronary circulation are different from those used in peripheral arteries.[24 25 27] They have a channel through the metal cap which allows the passage of a conventional angioplasty guide wire; this can be positioned across the stenosis before the optical fibre is advanced. The guide wire facilitates both positioning and centralisation of the metal cap. To minimise the effects of potential complications the procedure was performed at the time of coronary bypass surgery after pericardiotomy but before the institution of cardiopulmonary bypass.

Patients and methods

PATIENTS

Six patients (all men, aged 54–71, mean 59 years) with multivessel coronary disease and stable angina pectoris refractory to medical treatment who were referred for routine coronary artery bypass grafting were studied. All had a significant stenosis (from 70% to 80% reduction in internal lumen diameter) of the left anterior descending artery. Laser recanalisation of only this artery was attempted. Table 1 shows the clinical and angiographic details. The approval of the ethics committee and the written informed consent of patients were obtained.

PROTOCOL

After sternotomy, pericardiotomy, cannulation of the ascending aorta, and administration of heparin (300 IU/kg), a 9F arterial sheath was placed in the right femoral artery. The tip of a 9F guiding catheter was positioned, via the sheath, into the left coronary ostium and an angiogram was obtained. In the operating theatre angiography was recorded from fluoroscopy on to videotape; although the quality of the images was not as good as that provided by cineangiography, it was satisfactory for performing the procedure safely. A 0·012 inch diameter, 300 cm long Kaltenbach steerable guide wire was advanced across the left anterior descending artery using conventional angioplasty techniques and the stenosis was crossed. A 300 μm core optical fibre fitted with a 1·5 mm metal cap (Trimedyne Inc, Santa Ana, California) was coupled to an argon laser generator. Coupling and transmission efficiency, assessed before the procedure with a 300 μm bare optical fibre, was found to be 90%. The metal-capped end of the fibre (fig 1) was then advanced over the guide wire (accommodated in a tunnel through the metal cap) to the site of the stenosis in the left anterior descending artery. When no further advancement could be achieved, a 6 W laser pulse was delivered for 4–6 s (energy 24–36 J). During laser delivery gentle pressure was applied to advance the fibre through the stenosis. If the stenosis was not crossed further laser pulses of 8 W for exposure times of up to 8 s were delivered. After the stenosis had been crossed, the fibre was advanced during the cooling period for 1–2

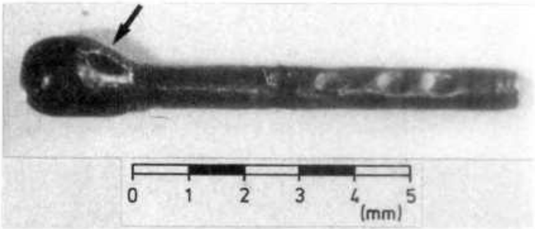

Fig 1 *Photomicrograph of the 1·5 mm metal-capped optical fibre. The arrow shows the entry point of the channel for the passage of the guide wire.*

Table 1 *Characteristics of six patients studied*

				Baseline angiography (% stenosis)		
Patient No	*Age/sex*	*Angina duration (y)*	*Basal ECG*	*LAD (%)**	*Cx (%)*	*RCA (%)*
1	61/M	2	Qw V1—V3†	80 (3 cm)	90	Normal
2	71/M	10	Normal	80 (3 cm)	Normal	90
3	60/M	2	Qw II–III aVF†	80 (1 cm)	Normal	90
4	54/M	11	Normal	80 (1 cm)	90	70
5	56/M	3	Normal	70 (1 cm)	70	90
6	56/M	10	Qw II–III aVF†	70 (1 cm)	100	80

Cx, circumflex artery; ECG, electrocardiogram; LAD, left anterior descending artery; Qw, Q wave; RCA, right coronary artery.
*Length of the stenosis is shown in parentheses.
†Myocardial infarction occurred 2–10 years before the study.

Table 2 *Values of laser energy delivered in six patients, effects on the severity of the left anterior artery stenosis, and complications*

Patient No	*Laser pulses (No)*	*Power (W)*	*Duration (s)*	*Energy (J)*	*Fibre progression*	*Repeat angiography*	
						LAD stenosis	*Acute complications*
1	1	6	4	24	No	Improved	None
	2	8	6	48	Yes		
	3	8	6	48	Yes		
	4	8	4	32	Yes		
	*5	10	10	100	Yes		
2	1	6	4	24	No	Unchanged	LAD Perforation
	2	8	6	48	No		
	3	8	5	40	No		
	4	8	10	80	No		
3	1	6	6	36	No	Improved	None
	2	8	3	24	No		
	3	8	3	24	Yes		
	*4	8	6	48	Yes		
4	1	6	6	36	No	Unchanged	None
	2	8	3	24	No		
	3	8	3	24	No		
5	*1	6	8	48	Yes	Unchanged	None
	*2	8	6	48	Yes		
6	1	6	6	36	Yes	Improved	None
	*2	8	4	32	Yes		

LAD, left anterior descending artery.
*Laser pulse delivered during fibre withdrawal.

seconds over a distance of approximately 1 cm to avoid adherence of the metal cap to the arterial wall. A laser pulse was also delivered during fibre withdrawal, with at least the same power that was used to cross the stenosis. Angiography was repeated after each laser pulse. At the end of the laser procedure cardiopulmonary bypass was started, an internal mammary artery graft was anastomosed to the left anterior descending artery, and saphenous vein grafts were inserted on to the remaining diseased coronary branches. Immediately after operation the heparinisation was reversed with protamine sulphate. In patients with successful laser recanalisation coronary angiography was repeated at 24 hours.

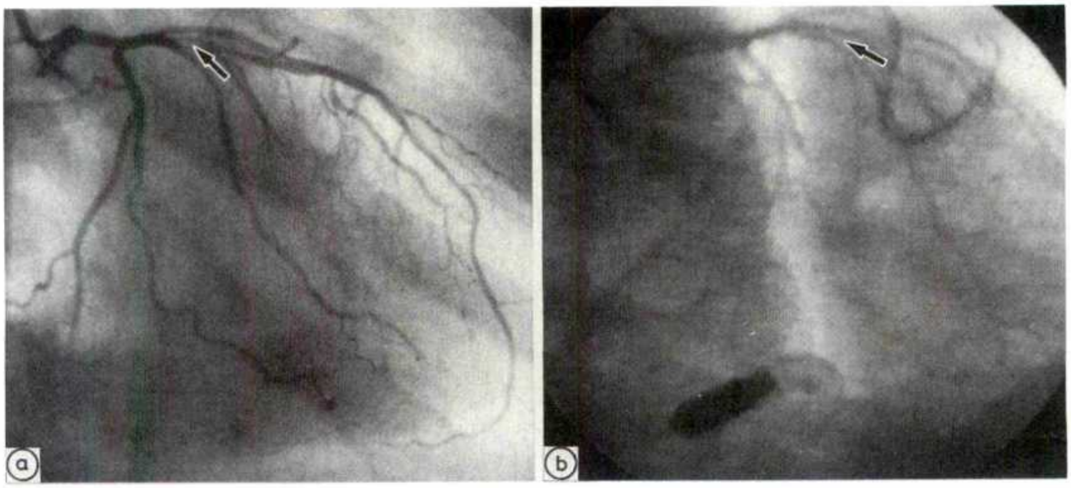

Fig 2 *(a) Baseline cineangiogram of patient 3 showing severe stenosis (arrow) of the left anterior descending artery. (b) Angiogram of the left coronary artery (obtained by recording the fluoroscopic image on videotape) immediately after the delivery of laser energy (132 J). A considerable reduction in the severity of the stenosis of the left anterior descending artery is apparent (arrow); the arterial wall does not show evidence of irregularities.*

Results

The laser procedure reduced the severity of the left anterior descending artery stenosis in three of the six patients. In patient 2 the delivery of > 112 J at the same site caused coronary perforation. Therefore, in the subsequent four patients the delivery of laser energy in the attempt to traverse the stenosis was limited to < 90 J. In all cases, inspection of the metal cap after the procedure showed the presence of charred blood which could be scraped off with a scalpel blade. The results are presented in detail below and are summarised in table 2.

SUCCESSFUL LASER RECANALISATION

In patient 1 the first laser pulse (24 J) did not allow the fibre to be advanced through a 3 cm long 80% stenosis. The following three laser pulses (48 J, 48 J, and 32 J) resulted in the gradual progression of the fibre across the stenosis. A 100 J laser pulse was delivered during withdrawal. Repeat angiography showed a reduction in the severity of the stenosis.

In patient 3 the initial two laser pulses (36 J and 24 J, respectively) did not allow advancement of the fibre through an 80% stenosis; this was achieved with the third 24 J laser pulse. In addition, 48 J was delivered during fibre withdrawal. In patient 6 a 70%

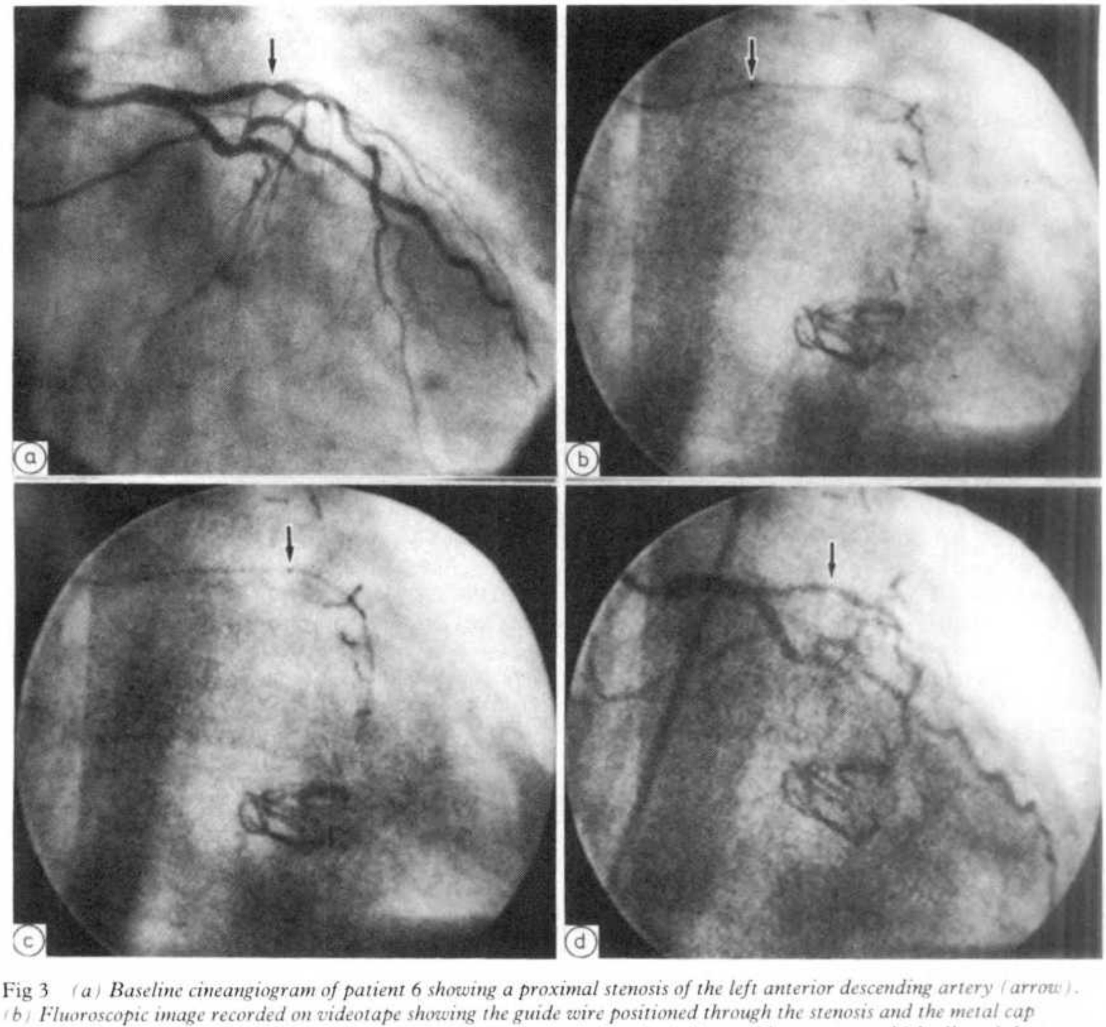

Fig 3 *(a) Baseline cineangiogram of patient 6 showing a proximal stenosis of the left anterior descending artery (arrow). (b) Fluoroscopic image recorded on videotape showing the guide wire positioned through the stenosis and the metal cap (arrow) proximal to the stenosis. (c) Fluoroscopic image obtained after the delivery of laser energy which allowed the passage of the optical fibre through the stenosis. The metal cap (arrow) is now distal to the stenosis. (d) Angiogram of the left coronary artery (obtained by recording the fluoroscopic image on videotape) immediately after the delivery of laser energy. There is considerable improvement in the severity of the stenosis (arrow).*

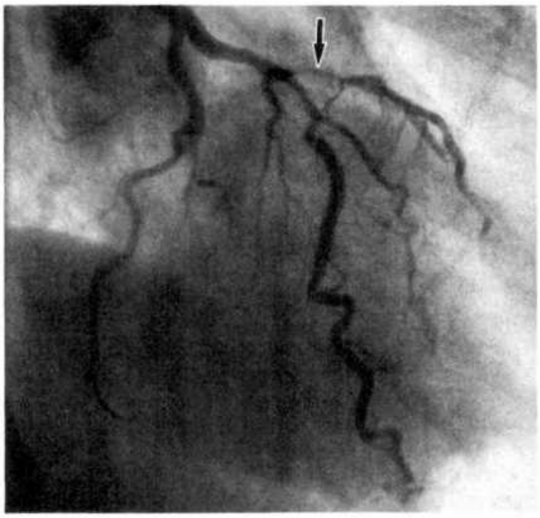

Fig 4 *Baseline cineangiogram of patient 2 showing a long severe calcific stenosis (arrow) of the left anterior descending artery. Four laser pulses (192 J) failed to permit the passage of the fibre through the lesion and resulted in perforation.*

stenosis was traversed with the first 36 J laser pulse; 32 J was delivered during fibre withdrawal. In both cases repeat angiography showed that the severity of the stenosis had been reduced (figs 2 and 3).

Angiography at 24 hours demonstrated a patent internal mammary graft in all three patients; in two of these there was total proximal occlusion of the left anterior descending artery.

UNSUCCESSFUL LASER RECANALISATION

In patient 2 the delivery of three laser pulses for a total of 112 J failed to allow progression of the fibre through a 3 cm long 80% calcific stenosis (fig 4). Repeat angiography at this stage did not show any complications. After the delivery of an additional 80 J laser pulse, angiography demonstrated periarterial contrast extravasation, indicating coronary perforation. Inspection of the artery showed a localised extravasation of blood contained within the epicardial fat and surrounding a minute perforation. Cardiopulmonary bypass was promptly instituted, the perforation was repaired with a single suture, and grafts were implanted in the normal way.

In patient 4 the fibre failed to cross an 80% stenosis despite the delivery of three laser pulses (total 84 J). During the attempts to advance the fibre, fluoroscopy showed bending of the fibre tip with a loss of alignment of the metal cap within the vessel lumen. Repeat angiography showed that the stenosis was unchanged. In patient 5 the fibre crossed a 70% stenosis before the delivery of laser energy. The two laser pulses (total energy 96 J) delivered during fibre withdrawal did not affect the severity of the stenosis.

In patients 2 and 4 the metal cap adhered to the arterial wall after the delivery of laser energy; a 1 s laser pulse at a power of 6 W was necessary in these cases to detach the fibre from the arterial wall.

Discussion

In this study percutaneous coronary laser recanalisation of a severe stenosis of the left anterior descending artery was attempted in six patients with metal-capped optical fibres at the time of coronary bypass surgery. In three patients the delivery of laser energy permitted the metal cap to cross the stenosis, and in all three a reduction in the severity of stenosis was confirmed at angiography. Multiple factors determined success or failure. The procedure was successful in patient 1 but not in patient 2, although in both the angiographic severity of the stenoses was similar. On direct observation and palpation during surgery, however, the stenosis in patient 2 was found to be much more tortuous and calcified than was suggested by angiography. It is possible that the heat generated by the metal cap was insufficient to vaporise the calcified component of the atherosclerotic plaque. In patient 4, although the stenosis was less severe than in patients 1 and 2, malalignment of the fibre within the vessel lumen probably accounted for the lack of success. In patient 5 the metal cap was too small for the size of the artery and no apparent improvement in the severity of the stenosis was obtained despite the laser energy delivered during withdrawal of the fibre through the stenosis.

This study confirms the experimental observation that circumferential distribution of thermal energy from metal-capped fibres is associated with a low risk of perforation.[24 25 27 28] It also provides information on the safety levels of laser energy which allow coronary recanalisation without perforation—although the precise threshold for perforation is still uncertain because it is difficult to quantify the amount of pressure applied to the optical fibre. Coronary perforation only occurred in one patient when 192 J was delivered at the same site, but not in the five other patients in whom < 90 J was used when the delivery of laser energy was not accompanied by fibre progression.

In this early series of patients, to minimise the risk of potentially serious complications the procedure was performed at the time of operation before cardiopulmonary bypass was started. The study design, therefore, does not assess medium and long term patency of treated vessels because occlusion of the left anterior descending artery (proximal to graft insertion) was favoured by the competitive flow from the graft, by the reversal of anticoagulation, and by the absence of antiplatelet treatment. In two studies percutaneous coronary laser recanalisation with metal-capped optical fibres was attempted as an adjunct to balloon angioplasty in closed chest patients.[29,30] Cumberland *et al* used this technique in four patients with a severe coronary stenosis that could only be crossed with a guide wire but not with a balloon catheter. Three of these four high risk patients developed myocardial infarction within 12 hours of the procedure; the mechanism of occlusion was not investigated.[29] In a later study in patients with less severe coronary stenoses Sanborn *et al* reported successful laser recanalisation in four of seven patients, apparently without acute complications.[30]

The low primary success rate and the potential problem of early occlusion indicate that this technique will have to be improved before percutaneous coronary laser recanalisation with metal-capped fibres can be recommended.

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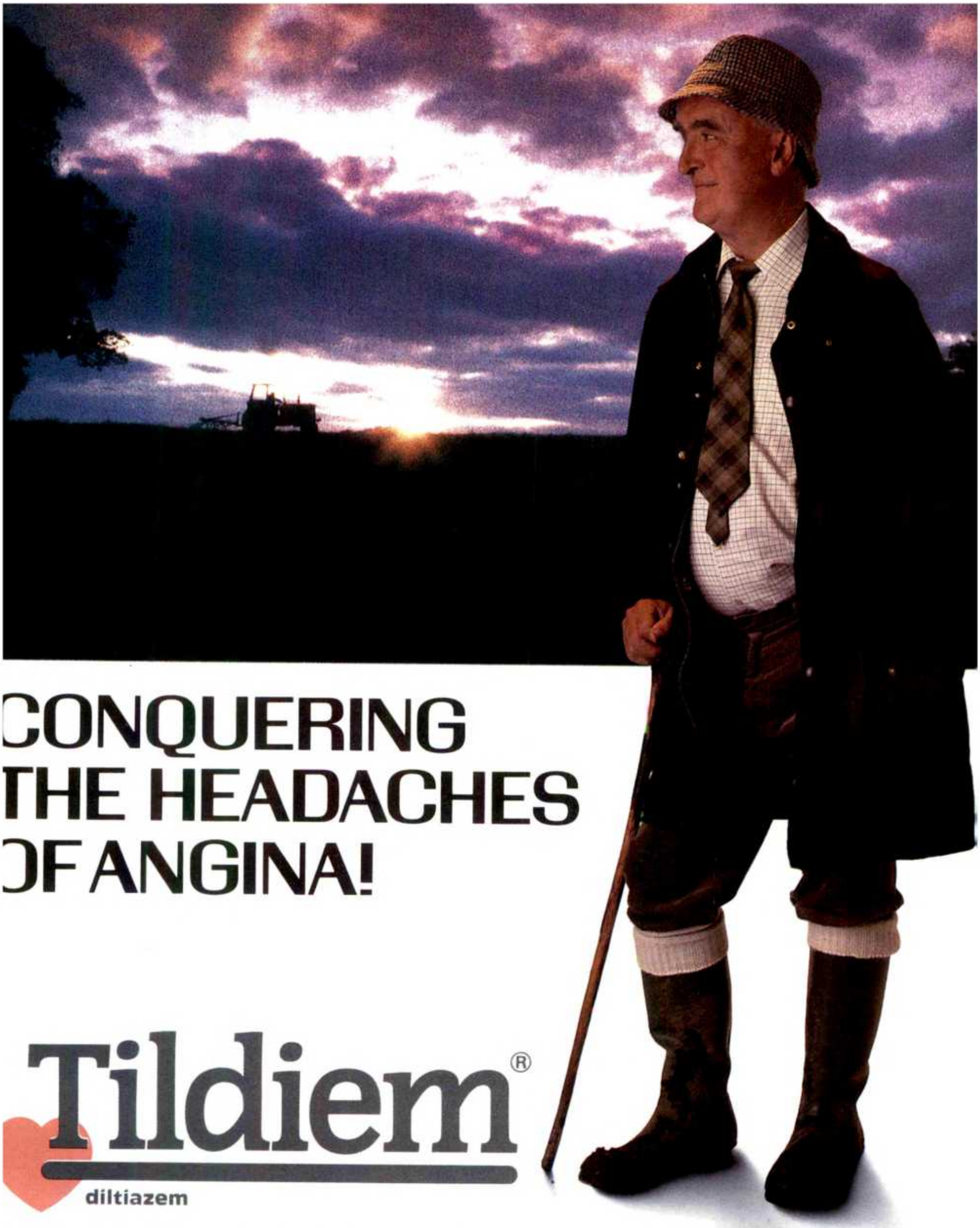

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Enzyme tests in the evaluation of thrombolysis in acute myocardial infarction

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SUMMARY The activity of α-hydroxybutyrate dehydrogenase, creatine kinase, creatine kinase MB and aspartate aminotransferase was measured on serial plasma samples from patients with acute myocardial infarction. The study was part of a multicentre randomised trial of the effect of thrombolytic treatment in the acute phase of acute myocardial infarction. The applicability and comparability of enzyme tests for the estimation of myocardial injury were studied in 76 control patients and 74 patients treated with streptokinase. Treatment with streptokinase caused a considerable acceleration of enzyme release after acute myocardial infarction, both in patients with persistent coronary occlusion and in those with successful reperfusion. But this changed pattern of enzyme release did not affect the rate of enzyme elimination from plasma or the released proportions of different enzymes.

Thus the assessment of infarct size by measurement of these enzyme activities can also be applied to patients treated with streptokinase. Moreover, the enzymes measured in the present study are all equally valid markers of myocardial injury.

The beneficial effects of early thrombolytic treatment in patients with acute myocardial infarction have been demonstrated in several large clinical trials.[1-6] Such treatment leads to patency of the infarct related coronary artery, limitation of infarct size, improved left ventricular function, and decreased mortality. These features are not equally reliable indicators of the efficacy of new thrombolytic agents, however. For example recanalisation of the coronary artery is not always associated with limitation of infarct size, improvement of left ventricular function, or decreased mortality.[5] Large clinical trials are needed to demonstrate improvement of left ventricular function or decreased mortality after thrombolytic treatment.[2 3] Smaller trials produced false negative results[7] as did earlier trials of low-dose intravenous streptokinase.[8 9] Negative results in some of these studies were the result of long delays before treatment and exclusion of patients with large areas of ischaemia, who have most to gain from early thrombolytic treatment.[5 6]

The most sensitive indicator in the evaluation of thrombolytic treatment is infarct size as estimated by the cumulative release of enzymes from the myocardium.[1 5 6 10] The usefulness of cumulative enzyme release as a marker of myocardial damage and the correlation of such estimates with necropsy data were shown in several studies.[11-14] But streptokinase profoundly influences the time course of enzyme release after acute myocardial infarction.[15 16] Such changes may reflect altered rates of enzyme elimination from plasma and this would invalidate comparison between streptokinase and other treatment. Accelerated washout of enzymes from the infarcted area could also influence the exposure of enzymes to denaturating conditions and could thus change the release of enzyme activity in plasma.[17-19] Such effects would also affect the proportions in which labile and stable enzymes are released.

We studied the validity of enzyme tests after thrombolytic treatment. Multienzyme analysis of plasma samples was included in the protocol of a large trial on the effects of streptokinase after acute

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myocardial infarction and time-activity curves of several enzymes were determined. These data were analysed by a method that simultaneously estimates the elimination rates from plasma of various enzymes and by calculation of cumulative release of these enzymes in the first few days after acute myocardial infarction.

Patients and methods

The study, carried out under the auspicies of the Netherlands Interuniversity Cardiology Institute, was part of a randomised controlled trial to compare early thrombolytic treatment with conventional treatment in patients with acute myocardial infarction. Full details on patient selection, treatment protocol, and clinical outcome in 269 treated patients and 264 controls have been published.[1, 2] Briefly, the procedures were as follows.

Patients with acute myocardial infarction aged ≤ 70 years were included in the trial if they were admitted to the coronary care unit within four hours of the onset of symptoms. The diagnosis of acute myocardial infarction was based on chest pain lasting > 20 minutes and electrocardiographic signs typical of myocardial infarction (that is ST segment elevation of at least 0·1 mV in a limb lead or 0·2 mV ST segment deviation in one of the precordial leads). Exclusion criteria included previous bypass surgery or treatment with streptokinase, recent bleeding or trauma, and inability to give informed consent. Eligible patients were registered by a telephone answering service which then allocated treatment. Only patients allocated to treatment with streptokinase were asked for informed consent and had angiography during the acute stages of infarction. When coronary anteriography showed that the infarct related artery was occluded or severely narrowed in the group allocated to thrombolysis, intracoronary streptokinase was infused at a rate of 4000 U/min to a maximum of 250 000 units. Patients randomised to treatment after January 1984 were given an intravenous bolus dose of 500 000 units of streptokinase before the intracoronary dose. Patients who had cardioversion were excluded because this procedure caused a considerable release of creatine kinase from injured skeletal muscle.

MEASUREMENT OF ENZYME ACTIVITIES

At all centres the activity of α-hydroxybutyrate dehydrogenase was measured in seven serum samples obtained in the first four days after acute myocardial infarction. In three of the five participating centres analysis of enzyme activity was more elaborate and samples were taken at the following times after admission to the coronary care unit: *University Hospital, Leiden:*—0, 4, 8, 12, 16, 20, 32, 44, 56, 68, 92, and 116 hours; *University Hospital, Maastricht*—0, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 60, 72, 84, and 96 hours; *Free University Hospital, Amsterdam*—0, 6, 12, 24, 36, 48, 72, and 96 hours.

We measured enzyme activity in serum samples kept at 4°C and assayed within 16 hours (Amsterdam) or plasma obtained by immediate centrifugation of blood samples for 15 minutes at 2500 rpm and stored at −20°C (Leiden and Maastricht).

The activity of α-hydroxybutyrate dehydrogenase was measured at 25°C with α-ketobutyrate as substrate[20] using a commercial test kit (Boehringer, HBDH-Optimiert) in Leiden and Maastricht. In Amsterdam, the activity of lactate dehydrogenase was assayed at 25°C according to the recommendations of the Dutch Association for Clinical Chemistry[21] and converted to α-hydroxybutyrate dehydrogenase activity as described in.[10]

Aspartate aminotransferase was assayed at 25°C with aspartate and α-ketoglutamate as substrates[22] with a test kit (Boehringer GOT-Optimiert) in Leiden and Maastricht and by another assay method in Amsterdam.[21]

Creatine kinase was measured at 25° with creatine phosphate as substrate[23] with test kits (that is Boehringer CPK-Optimiert in Leiden and Merck CPK-NAC in Maastricht) and at 30°C by another assay method in Amsterdam.[21]

Creatine kinase isoenzyme MB was determined by immunochemistry[24] using test kits (Boehringer CPK-MB Monotest) at 30°C in Amsterdam and 25°C in Leiden and Maastricht.

Ezyme activities were expressed in units per litre (U/l). One unit of activity converts one μmol of substrate per minute at the indicated temperature. Systematic differences in enzyme activities introduced by the use of different assay conditions at different centres were eliminated by comparison against standards. The activities of α-hydroxbutyrate dehydrogenase measured in Leiden and Maastricht, for instance, were multiplied by a factor of 1·34. Final mean (SD) activities (U/l) in normal plasma were: α-hydroxybutyrate dehydrogenase 126 (21); creatine kinase 39 (19); aspartate aminotransferase 10 (3); and creatine kinase MB 4·4 (2·3). The enzyme content of cytoplasm from human myocardial biopsy specimens, expressed in units per gram wet weight of tissue (U/g), determined by the same assay conditions was as follows (mean (SD))[25 26]: α-hydroxybutyrate 165 (15); creatine kinase 865 (87); aspartate aminotransferase 54 (6); creatine kinase MB 132 (36). These latter values were used to express cumulative release of enzymes in gram equivalents of myocardium (see below).

CALCULATION OF CUMULATIVE RELEASE OF ENZYMES

Time-activity curves were analysed according to the two-compartment model (fig 1), that has been validated in many studies on the turnover of radiolabelled plasma proteins and circulating tissue enzymes.[27] The plasma activity of enzyme C at time t is determined by input of enzyme from the heart and elimination of enzyme determined by a fractional catabolic rate constant (FCR). In addition, there is extravasation of enzyme (measured by a fractional transcapillary escape rate constant (TER)) and return to plasma from the extravascular pool E(t) (measured by a fractional extravascular return rate constant (ERR)). Cumulative release of enzyme per litre of plasma from zero time up to time t is given by:

$$Q(t) = C(t) + E(t) + \int_0^t FCR.C(\tau)d\tau \qquad (1)$$

where C(t) and E(t) are the activities still present in intravascular and extravascular spaces and the integral term encompasses eliminated activity. The extravascular pool E(t) is determined by the time-dependent plasma activity and TER and ERR[28]:

$$E(t) = TER.\exp(-ERR.t).\int_0^t \exp(ERR.\tau)C(\tau)d\tau \qquad (2)$$

Values of C(t) in equations (1) and (2) were obtained by subtraction of the normal activities in plasma from the actual activities measured at time t. Individual values of these normal activities were estimated from the first sample of each patient. Fixed values of TER = 0·014 per hour and ERR = 0·018 per hour were used for all enzymes.[27 28]

ESTIMATION OF FRACTIONAL CATABOLIC RATE CONSTANTS (FCR)

Values of FCR for creatine kinase, creatine kinase-MB, and aspartate aminotransferase were estimated as described elsewhere.[28] The procedure is based on the comparison of the time-activity curve of one enzyme with a simultaneously measured curve of a slowly eliminated reference enzyme. Comparisons were performed over a period of 48 hours after first symptoms (t = 0), using α-hydroxybutyrate dehydrogenase as the reference enzyme. This technique was validated by intravenous infusion of enzymes in the dog[28] and yields the value of FCR as well as the ratio of released quantities of reference enzyme and the test enzyme (ρ_{CK} = released α-hydroxybutyrate dehydrogenase (HBDH) activity/released creatine kinase activity). It should be noted that the values of ρ thus obtained are mainly determined by the initial increases of both time-activity curves. These values may deviate to some extent from the calculated ratios of enzyme release. For instance ρ_{CK}, obtained from the estimation procedure, may differ from Q_{HBDH}/Q_{CK} calculated from equation (1) and (2) for longer intervals.

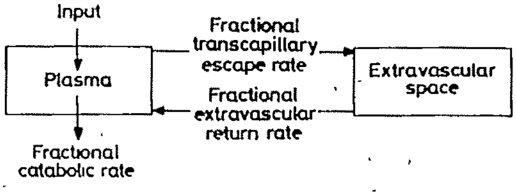
Input
Plasma
Fractional transcapillary escape rate
Extravascular space
Fractional extravascular return rate
Fractional catabolic rate

Fig 1 *Two-compartment model for circulating proteins.*

Results

Table 1 shows the distribution of patients with complete time-activity curves up to at least 48 hours after acute myocardial infarction. Data for some patients were incomplete because of death, early surgery or percutaneous transluminal coronary angioplasty, or refusal of informed consent after allocation to thrombolytic treatment.

Figure 2 shows the plasma curves obtained from the three participating centres. The small number of patients from Leiden explains an increased variability in the right hand panel. Figure 2 shows that results from the three centres were similar and that it was acceptable to pool data. Early release of all enzymes was accelerated in the patients treated with streptokinase. This was further investigated by calculating the time t_h at which cumulative release of enzyme equalled half of the total quantity released ($Q(t_h) = Q(48)/2$). Accelerated release implies an earlier t_h and fig 3 shows that this was indeed found in patients treated with streptokinase. In all three groups treated with streptokinase t_h was significantly different from controls ($p < 0{\cdot}001$, Mann-Whitney). It is interesting to find that early release was also increased in patients with unsuccessful thrombolysis. Apparently, the effect is not dependent on early coronary reperfusion.

Estimation of the fractional catabolic rate constants for creatine kinase, creatine kinase-MB, and aspartate aminotransferase is based on a fixed value of 0·015 per hour for α-hydroxybutyrate dehydrogen-

Table 1 *Distribution of patients*

	Maastricht		*Amsterdam*		*Leiden*	
	SK	*C*	*SK*	*C*	*SK*	*C*
Entered in the trial	61	62	47	46	9	10
Complete enzyme data	47	47	31	37	4	7
Rejected because of cardioversion	3	4	4	10	1	1
Entered in the present study	44	43	27	27	3	6

SK, streptokinase; C, controls.

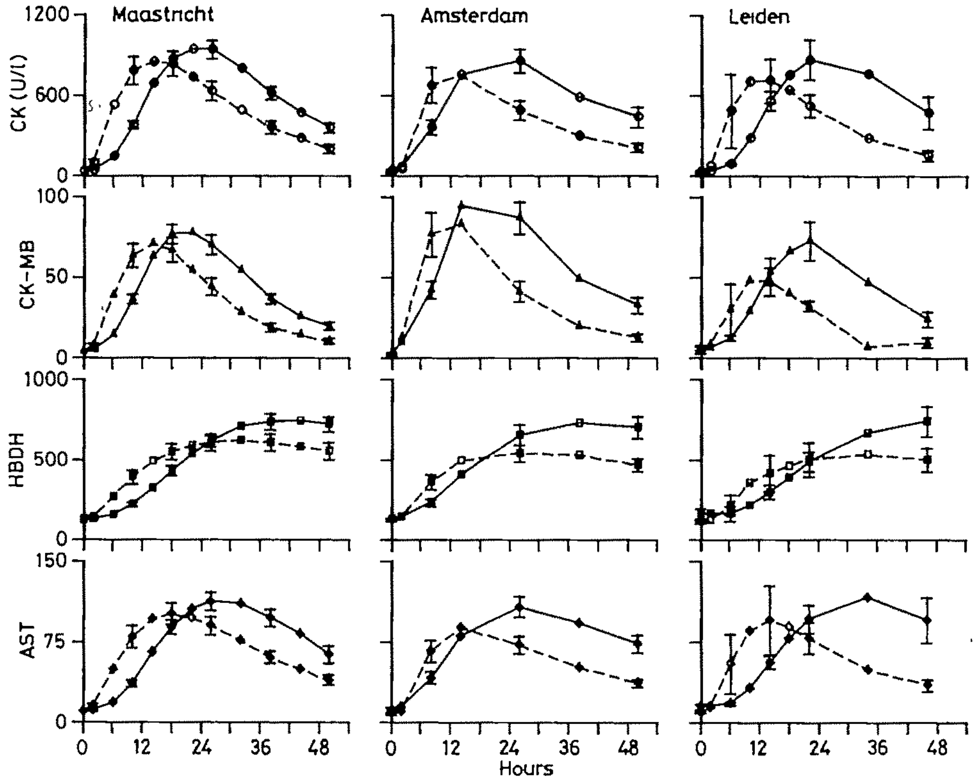

Fig 2 *Mean (SEM) time-activity curves obtained at the three participating centres. Broken lines indicate patients treated with streptokinase and continuous lines indicate the controls. K, creatine kinase; HBDH, α-hydroxybutyrate dehydrogenase; AST, aspartate aminotransferase.*

ase as estimated in patients with acute myocardial infarction.[29] In order to check whether this value can also be used in patients treated with streptokinase the apparent fractional disappearance constant (k_d) of α-hydroxybutyrate dehydrogenase from plasma was estimated in both groups between 72 and 96 hours after acute myocardial infarction. Mean (SD) values of k_d = 0·0097 (0·0001) per hour and k_d = 0·0094 (0·0002) per hour respectively were found in 60 controls and in 54 patients treated with streptokinase. This difference is not statistically significant. This value of k_d is lower than the fractional catabolic rate for α-hydroxybutyrate dehydrogenase because enzyme release tails off and there is extravascular return of the enzymes during the elimination phase.[27] Table 2 shows the values of the fractional catabolic rate and ρ. Patients with a cumulative release equivalent to $\leqslant$300 U/l of α-hydroxybutyrate dehydrogenase activity in the first 48 hours after acute myocardial infarction (n = 21) were omitted because such small infarctions produce ill-defined curves with unreliable values. Six patients with a creatine kinase activity of $\geqslant$100 U/l in the first sample were also omitted because infarctions in these patients may have occurred more than four hours

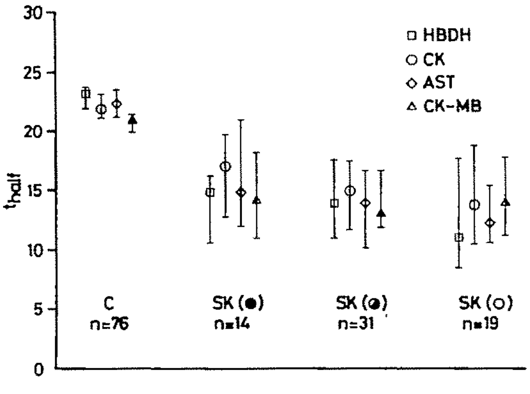

Fig 3 *Median values and 95% confidence intervals for the time needed to reach half of the total release in 48 hours. C, controls; SK, streptokinase group. (●) Persisting total occlusion; (◑) reperfusion with more than 90% stenosis remaining; and (○) reperfusion with < 90% stenosis remaining. See legend to fig 2 for abbreviations.*

Table 2 *Mean (SEM) results of the estimation procedure with HBDH as the reference enzyme*

	Controls (n = 67)	*Thrombolysis (n = 58)*
FCR_{CK}	0·19 (0 02)	0·19 (0 02)
FCR_{AST}	0 082 (0·006)	0·090 (0 007)
$FCR_{CK\text{-}MB}$	0 37 (0 07)	0 38 (0 07)
ρ_{CK}	0 19 (0 01)	0 18 (0·01)
ρ_{AST}	2 95 (0 11)	2 76 (0·12)
$\rho_{CK\text{-}MB}$	1·27 (0 17)	1 21 (0·14)

FCR_{HBDH} equals 0 015 per hour.[29] Values of ρ in human myocardium are ρ_{CK} = HBDH/CK = 0 19, ρ_{AST} = HBDH/AST = 3 05 and $\rho_{CK\text{-}MB}$ = HBDH/CK-MB = 1 25.

before the first sample was obtained. It follows from the values presented in table 2 that despite the considerably altered time course of enzyme release after streptokinase (see fig 2) both groups had identical values for fractional catabolic rate and ρ. Values of ρ in table 2 are approximately equal to the values calculated from the cytoplasmic enzyme content of myocardium. This implies that estimates of injury from different enzymes will be similar if the released quantities are expressed in gram-equivalents of myocardium. Figure 4 shows the result of this calculation in both groups of patients. The overall reduction of enzyme release after treatment with streptokinase that has been reported for α-hydroxybutyrate dehydrogenase was also apparent for the other enzymes. Although creatine kinase-MB somewhat underestimated and aspartate aminotransferase somewhat overestimated the infarct size calculated from α-hydroxybutyrate dehydrogenase and creatine kinase, this figure shows that there is a global release of cytoplasmic enzymes that reflects their proportions in the myocardium. More importantly, it also shows that streptokinase does not influence the proportions in which the various enzymes are released.

Release of α-hydroxybutyrate dehydrogenase and creatine kinase-MB was faster in the treated group than in the controls and the reduction of enzyme release by streptokinase only became apparent after 36 hours (fig 5).

Figure 6 shows the relations between estimates of myocardial damage based on different enzymes. The strongest correlations were found between α-hydroxybutyrate dehydrogenase and aspartate aminotransferase (r = 0·95 and r = 0·89 in streptokinase and control groups respectively) but creatine kinase and creatine kinase-MB also correlate well with α-hydroxybutyrate dehydrogenase (r = 0 73–0·89). This implies that estimates of myocardial injury can in principle be based on any of the enzymes studied. The choice of specific marker enzymes may be decided by considerations such as those of convenience, specificity, and accuracy.[26 30–32] Again this situation was not changed by treatment with streptokinase, despite the somewhat steeper slope of the regression line for the treated group in the creatine kinase panel of fig 6. The ratio of α-hydroxybutyrate dehydrogenase to creatine kinase release is identical in both groups (fig 4) and the changed slope in fig 6 is an effect of the non-uniform distribution of data.

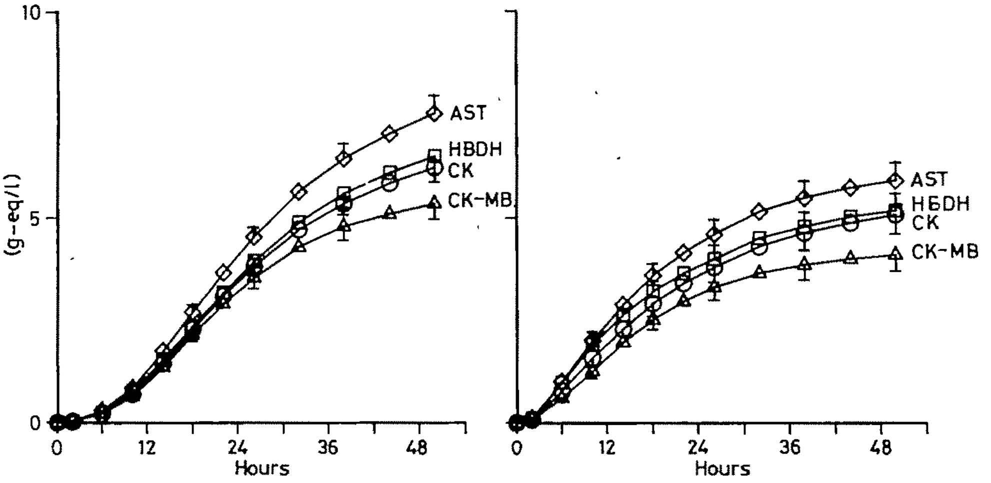

Fig 4 *Mean infarct size assessed by enzyme activity (expressed as gram-equivalents of myocardium per litre of plasma) based on cumulative release of HBDH (□), CK (○), AST (△), and CK-MB (△) after treatment with streptokinase (right panel) and in controls (left panel). See legend to fig 2 for abbreviations.*

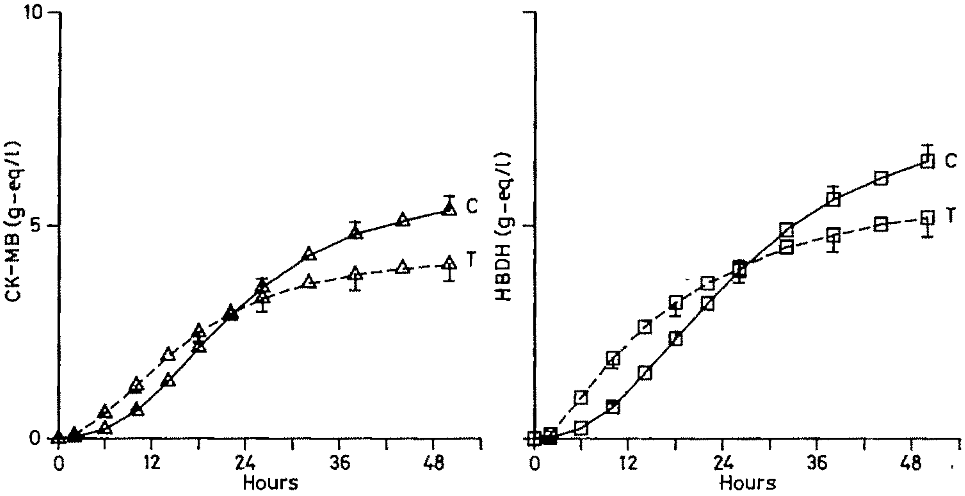

Fig 5 *Mean infarct size assessed by enzyme activity (expressed in gram-equivalents of myocardium per litre of plasma) and based on cumulative release of HBDH and CK-MB. Broken lines indicate patients treated with streptokinase and continuous lines indicate controls. See legend to fig 2 for abbreviations.*

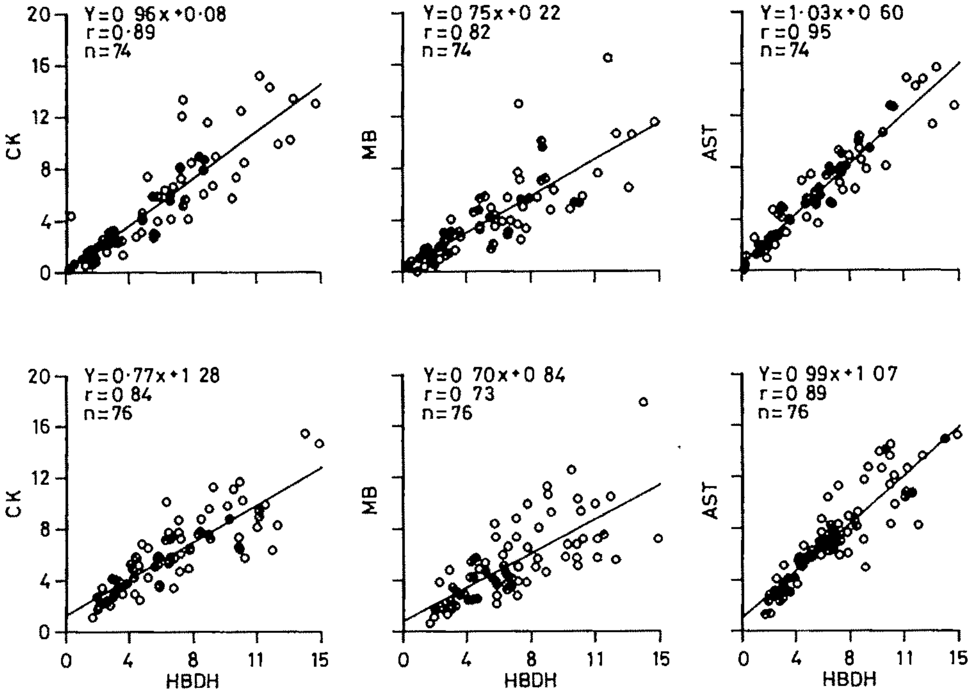

Fig 6 *Correlations between infarct size assessed by enzyme activity (expressed in gram-equivalents of myocardium released per litre of plasma during the first 48 hours) calculated for different enzymes. Upper figures are for patients treated with streptokinase, lower figures are controls. See fig 2 for abbreviations.*

Discussion

Rapid release of aspartate transaminase, shown by early peak activities in plasma, was noted the first time that patients with acute myocardial infarction were treated with streptokinase.[15] Since then the effect has been reported for creatine kinase[16] and lactate dehydrogenase[33] and after the administration, of urokinase.[34] Early investigators ascribed this phenomenon to accelerated wash-out of enzymes from the infarcted area caused by reperfusion. Later on the phenomenon of "reperfusion damage" became apparent: reperfusion of the myocardium after temporary ischaemia may result in a paradoxical exacerbation of cellular damage, associated with an immediate release of intracellular enzymes.[35 36] Accelerated wash-out probably contributes only marginally to this effect because it was also seen after reoxygenation of hypoxic monolayer heart cell cultures.[37] In these preparations typical wash-out effects can be excluded. So reperfusion seems to result in more rapid necrosis, probably of myocardial tissue that has already been irreversibly damaged.

Reperfusion obviously occurs after spontaneous coronary reopening or successful thrombolysis—that is in 85% of the patients treated with streptokinase in the original trial[2]—and this could explain the early release of enzymes in the treatment group (fig 2). In fact, early peaking of creatine kinase activities has even been regarded as proof of successful reperfusion.[38-40] Figure 3, however, shows that such early release also occurs in patients with persistence of coronary occlusion after treatment with streptokinase. One explanation for this observation is that reperfusion occurred in most of these patients in the first few hours after the end of coronary catheterisation. In five of these patients, however, persisting coronary occlusion was demonstrated before discharge from hospital and the median values of t_h for α-hydroxybutyrate dehydrogenase, creatine kinase, creatine kinase-MB, and aspartate aminotransferase were 12·9 h, 17·0, 14·3 h, and 13·3 h respectively—not different from the values in fig 3. These findings suggest that streptokinase may have other effects as well as a thrombolytic action, which are responsible for accelerated enzyme release. A similar conclusion follows from some experimental studies in which streptokinase had a protective effect on the myocardium during non-thrombogenic hypoxia and ischaemia.[41 42] One of these studies showed that streptokinase had a vasodilatory effect on the non-ischaemic isolated rat heart.

Theoretically, early peaking of plasma enzyme activities, as shown in fig 2, could also be the result of an increase in the fractional catabolic rate after treatment with streptokinase. This would be a serious complication because the reported reduction of enzyme release in the patients treated with streptokinase[2 10] could be an artefact caused by underestimation of the fractional catabolic rate. This is why we analysed the effect of streptokinase on fractional catabolic rate. Estimation of fractional catabolic rate, however, is based on the assumption that myocardial enzymes are released simultaneously. A theoretical analysis showed that a delay of two hours between the release of α-hydroxybutyrate dehydrogenase and creatine kinase would produce a 50% error in values of fractional catabolic rate and ρ.[27] But a delay was not found in studies of experimental hypoxia or ischaemia in heart cell culture, isolated hearts, and hearts in situ: creatine kinase, aspartate aminotransferase, and α-hydroxybutyrate dehydrogenase were released in parallel.[27] It seems that the onset of permeability of the sarcolemma to cytosolic proteins is an all-or-none phenomenon. The validity of the estimation procedure was confirmed when ρ values accorded with myocardial enzyme content (table 2). Increases in enzyme activities in the plasma during the first few hours after acute myocardial infarction, when the role of extravasation and catabolism of enzymes is still minor, were also proportional to myocardial enzyme content.[29] Finally, any delay between the release of, say, creatine kinase and α-hydroxybutyrate dehydrogenase would probably be altered by the more rapid release after treatment with streptokinase and this would produce different values in the streptokinase and control groups; as the results in table 2 show, this did not happen.

In several clinical studies necropsy has shown highly significant correlations between infarct size and the release of creatine kinase (and creatine kinase-MB) in plasma.[11-13] A similar result was obtained for the release of lactate dehydrogenase.[14] Moreover, the reduction in α-hydroxybutyrate dehydrogenase activity in the heart was equivalent to the increase in plasma activity[26] and the results shown in fig 4 confirm this relation for other enzymes as well. Figures 4 and 6 show that after acute myocardial infarction various enzymes are released in fixed proportions that are independent of thrombolytic treatment. This implies that several validation studies[11-14] are relevant to the enzymes we studied. It is important to note that the release in plasma in some of these studies was seriously underestimated because the apparent disappearance constant k_d was used in the calculations instead of the fractional catabolic rate constant.[26]

The two main conclusions of the present study—that (a) infarct size is independent of the enzyme chosen for estimation and (b) thrombolytic treatment does not affect the values of fractional catabolic rate and ρ—imply that any of the enzymes studied is an equally valid marker of myocardial injury and each can be used for the evaluation of thrombolytic treatment. α-hydroxybutyrate dehydrogenase was chosen as the reference enzyme in the original trial[2,10] because of its slow elimination from plasma—that is, low fractional catabolic rate—which permitted cumulative release to be calculated accurately from a few samples.[31] A potential hazard is the occurrence of bleeding. Infarct size would be considerably overestimated if α-hydroxybutyrate dehydrogenase activity from extravasated erythrocytes entered the plasma. Estimates based on α-hydroxybutyrate dehydrogenase were similar to those based on creatine kinase and aspartate aminotransferase, however, and neither of these enzymes are found in erythrocytes. The strong correlation between α-hydroxybutyrate dehydrogenase and aspartate aminotransferase ($r = 0{\cdot}95$) in the streptokinase group (fig 6) in which bleeding was frequent, precludes any important release of α-hydroxybutyrate dehydrogenase from erythrocytes.

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Prognosis and thallium-201 scintigraphy in patients admitted with chest pain without confirmed acute myocardial infarction

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SUMMARY Exercise and rest thallium scintigraphy and exercise electrocardiography were performed after discharge in 158 patients aged <76 years admitted with chest pain in whom a suspected diagnosis of acute myocardial infarction had not been confirmed. During a follow up of 12–24 months (median 14 months) there were 10 cardiac events—that is, non-fatal acute myocardial infarction or cardiac deaths. Transient thallium defects and abnormal ST response (that is ST segment deviation or uninterpretable ST segment) during exercise were correlated significantly with an unfavourable prognosis. One hundred and four patients with neither of these characteristics were at lower risk of a cardiac event than the 19 patients with both of these characteristics. The percentages of patients in these two groups without a cardiac event after one year were 98·1 and 78·8 respectively.

Thallium scintigraphy, alone or in combination with exercise electrocardiography, can be used to identify groups at high and low risk of future cardiac events, in patients with chest pain in whom acute myocardial infarction is suspected but not found.

Patients admitted with suspected acute myocardial infarction in whom the diagnosis is not confirmed have a high risk of cardiac events after discharge.[1-3] The risk is almost as great as it is in patients discharged after a confirmed myocardial infarction.[1 2] A method for identifying subgroups of high and low risk patients without acute myocardial infarction would be clinically useful. High risk patients could be considered for further investigations or close follow up, whereas low risk patients could be reassured about their prognosis.

Thallium scintigraphy at rest and during exercise is a sensitive and specific predictor of ischaemic heart disease.[4 5] It has been used to identify high risk groups in patients with chest pain,[6 7] and in patients with recent acute myocardial infarction.[8 9] The purpose of this prospective study was to evaluate whether thallium scintigraphy alone or in combination with exercise electrocardiography could identify high and low risk groups of patients admitted with chest pain without confirmed myocardial infarction.

Patients and methods

One hundred and fifty eight patients admitted with suspected acute myocardial infarction in whom this diagnosis was not confirmed were examined by exercise and rest thallium scintigraphy and exercise electrocardiography. Figure 1 shows that in a one year period (November 1 1981 to October 31 1982) 975 patients, residents of Frederiksborg County, Denmark, were admitted at least once with a suspected acute myocardial infarction to one of the four

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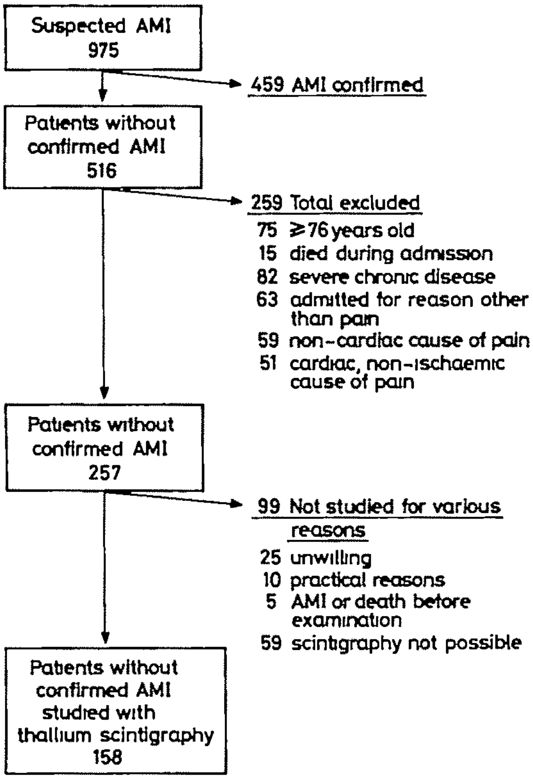
Suspected AMI
975
459 AMI confirmed
Patients without confirmed AMI
516
259 Total excluded
75 ≥76 years old
15 died during admission
82 severe chronic disease
63 admitted for reason other than pain
59 non-cardiac cause of pain
51 cardiac, non-ischaemic cause of pain
Patients without confirmed AMI
257
99 Not studied for various reasons
25 unwilling
10 practical reasons
5 AMI or death before examination
59 scintigraphy not possible
Patients without confirmed AMI studied with thallium scintigraphy
158

Fig 1 *Flow chart showing patients admitted with chest pain, without confirmed acute myocardial infarction who were assessed by thallium scintigraphy and exercise electrocardiography.*

coronary care units in the county. The suspicion of acute myocardial infarction was raised by the registrar on duty or by a general practitioner. Acute myocardial infarction was suspected if the patient had one or more of the following complaints: pain (that is, pain, pressure, or discomfort in chest, arms, or jaw for at least 20 minutes), severe dyspnoea, pulmonary oedema, cardiac arrest, electrocardiographic changes indicative of acute myocardial infarction, or syncope.

Acute myocardial infarction was confirmed in 459 patients (fig 1) who fulfilled at least one of the following three criteria: (*a*) an increase in cardiac enzymes (that is lactate dehydrogenase > 8·34 µkat/l; normal upper limit 7·09 µkat/l and/or aspartate aminotransferase > 0·83 µkat/l; normal upper limit 0·67 µkat/l); (*b*) electrocardiographic changes with development of Q wave or ST–T displacement or T wave inversion lasting > 48 hours; (*c*) positive evidence of acute myocardial infarction at necropsy. If none of the above laboratory criteria were fulfilled acute myocardial infarction was not confirmed. Of the 516 patients without confirmed acute myocardial infarction, 259 were excluded because of one or more of the following exclusion criteria (fig 1): (*a*) age > 75 years at admission; (*b*) death during admission; (*c*) severe chronic disease other than ischaemic heart disease (cancer, chronic pulmonary disease, sequelae of stroke, disability preventing investigations, for example arthritis); (*d*) admission for reasons other than pain; (*e*) confirmed non-cardiac aetiology of chest pain, for example pulmonary embolism, pleuro-pneumonia, ulcer, musculoskeletal pain; (*f*) important non-ischaemic heart disease, for example valvar heart disease, pericarditis, cardiomyopathy, arrhythmias. Ninety nine patients were not examined for various reasons (fig 1), including 59 patients in whom thallium scintigraphy was not possible because time for examination on the gamma-camera was limited, problems with delivery of thallium, or technical difficulties during the study.

Thus finally 158 patients who had been admitted with chest pain had thallium scintigraphy and an exercise test. The study was accepted by the regional ethics committee. Thirty eight (24%) of the patients were women and their median age was 56·7 years (range 32–75 years). Fifty nine patients had a history of angina pectoris and 34 of previous acute myocardial infarction.

Exercise electrocardiography combined with thallium scintigraphy was performed on the day of discharge or within four weeks of discharge. Exercise electrocardiography was performed three hours after the morning meal; the participants had not smoked or taken glyceryl trinitrate in this period. After 10 minutes of supine rest a 12 lead electrocardiogram was recorded. During exercise, leads V2, V4, and V6 were continuously recorded on paper at 10 mm/s and every minute at 50 mm/s for at least 15 s.

A symptom limited exercise test was performed on an electrically braked ergometer. The initial workload was 50 W except in a few patients where it was 25 W. The workload was increased by 50 (or 25) W every three minutes until the patient had to stop. ST segment changes during exercise were coded as: (*a*) normal; (*b*) ST deviation—that is elevation above 0·1 mV; ST depression at J point with horizontal or downsloping ST segment of 0·1 mV or more; and (*c*) uninterpretable—that is left bundle branch block at rest or development of left or right bundle branch block during exercise; ST segment depression combined with either depression at rest, left ventricular hypertrophy, right bundle branch block, left hemiblock, or digoxin treatment. An abnormal exercise electrocardiogram was defined as ST segment deviation (*b*) or uninterpretable (*c*).

Thallium chloride (2 m Ci) was injected intravenously one minute before the patients stopped exercising. Imaging was performed 5–10 minutes after the end of exercise and repeated after four hours.

Three images were acquired in 64 × 64 matrices with a GE Maxicamera large field of view: these were in anterior and left anterior oblique projections at 45° and 65°. A zoom factor of 1·4 was used and 350 000 counts were registered in the matrices. The total radiation exposure was approximately 140 mrad. The scintigrams were processed on a DEC gamma-11 system by a quantification procedure developed at the Thoraxcenter.[10] The orientation of the redistribution images was adjusted for rotation and translation with respect to the corresponding exercise images by interaction with the computer system until the same orientations were obtained visually. After automated left ventricular contour detection and interpolative background subtraction, circumferential profiles were computed at 6° intervals. The profiles of the exercise and redistribution images were normalised for the maximal value in the immediate post-exercise images (100%) excluding the outflow tract of the left ventricle. The analogue pictures from the gamma camera, the processed images, and the circumferential profiles were analysed by three independent observers without knowledge of the clinical or exercise electrocardiographic data. The interpretations of the three observers were compared and disagreement was resolved by consensus.

The thallium uptake in a total of nine segments in the three views was scored as normal or abnormal in the immediate post-exercise and redistribution images. The following segments were defined: posteroinferior, apical, and anterior in the anterior view; anteroseptal, apical, and posterolateral in the left anterior oblique 45° view; and anterior, apical, and inferoposterior in the left anterior oblique 65° view. The scintigrams were considered to show: (*a*) persistent defects if one or more segments showed abnormal areas without redistribution, (*b*) transient defects if one or more areas were initially abnormal, but later showed redistribution, or (*c*) normal uptake if both images were normal in all three views. The total number of permanent or transient defects and the locations were also calculated.

FOLLOW UP

The patients were followed from 12 to 24 months (median 14 months). Information on death was complete. It was obtained from the National Person Registration Office; in these cases further information was obtained from hospital records or death certificates. Information about acute myocardial infarction was obtained from the County Central Registry, which contains information on all hospital admissions in the county. To cover the possibility of patients suffering an acute myocardial infarction outside the county all patients were sent one questionnaire and one reminder. Ninety five per cent answered the questionnaire. All recorded acute myocardial infarctions occurred in the county.

STATISTICAL ANALYSIS

In the failure-time analysis a cardiac event was used as the end point. Non-cardiac deaths were excluded and only the first appearance of a cardiac event was considered. The probability of a cardiac event-free period after discharge was estimated by the Kaplan-Meier method, corrected for possible delayed entry.[11 12] The patients were considered to be at risk from the time of investigation until a cardiac event or censoring (or from time of discharge if the investigation was performed before discharge). The estimated cardiac event-free curves for groups were compared by the log-rank test.[12]

Results

FOLLOW UP

During follow up there were 10 cardiac events in the patients in whom exercise electrocardiography and thallium scintigraphy were performed. These were eight non-fatal acute myocardial infarctions, one fatal acute myocardial infarction, and one sudden death. Five events occurred within three months.

Eight cardiac events occurred in the 59 patients scheduled for thallium scintigraphy in whom the procedure could not be performed for reasons mentioned earlier (fig 1). The prognosis for these patients was slightly worse than it was in the 158 patients in whom thallium scintigraphy was performed ($p < 0.05$).

THALLIUM SCINTIGRAPHY

Thallium scintigraphy was normal in 97 (61·4%) patients. Persistent defects were found in 48 (30·3%) patients; the location was anterior in seven, posterolateral in 35, both in four, and apical only in two patients. Transient defects were recorded in 29 (18·3%) patients; the location was anterior in six, posterior in 14, and both in nine patients. Sixteen (10·1%) patients had both transient and persistent defects; 61 patients (38·6%) had either or both.

The table shows the prognosis in relation to thallium scintigraphy. A transient defect was a very sensitive predictor of later cardiac events (fig 2), whereas persistent defects were not. An abnormal

Table *Results of thallium scintigraphy and exercise electrocardiography and later cardiac events*

	Total No	*No with CE**	*1 year % without a CE†*	*p‖*
All patients	158	10	—	—
		Thallium scintigraphy		
Persistent defects:				
No	110	6	93·8	0·506
Yes	48	4	94·4	
Transient defects:				
No	129	4	97·8	0·001
Yes	29	6	82·6	
Combined:				
No defect	97	2	97·8	0·001
Transient only	13	4	69·2	
Persistent only	32	2	93·8	
Both	16	2	93·8	
Transient, persistent defect, or both	61	8	88·5	0·005‡
		Exercise electrocardiography		
Normal	114	3	97·3	0·005
ST deviation	20	3	84·5	
Uninterpretable	24	4	87·5	
ST deviation or uninterpretable	44	7	86·1	0·001§
		*Thallium scintigraphy and exercise electrocardiography combined***		
Both tests normal	104	2	98·1	0·001
Either test abnormal	35	3	90·9	
Both tests abnormal	19	5	78·8	

*CE, cardiac event

†Kaplan-Meier estimate of percentage without a cardiac event after one year follow up.

‡compared with "no defect";

§compared with "normal exercise electrocardiogram".

‖Log-rank test for comparison of survival curves during the whole follow up period.

**Abnormal exercise test includes ST deviation or uninterpretable ST segment.

scintigram, that is one showing transient, persistent, or combined defects, identified eight out of 10 patients with later cardiac events. Neither the number of areas with scintigraphic abnormalities nor their location gave further prognostic information.

EXERCISE ELECTROCARDIOGRAPHY

The exercise electrocardiogram was normal in 114 patients. ST deviation was seen in 20 patients. Four patients had ST elevation, 11 had 0·1–0·2 mV ST depression, and five patients had ST depression of ≥0·2 mV. The exercise electrocardiogram was uninterpretable in 24 patients (see Patients and Methods). The table shows the prognosis in relation to exercise electrocardiography.

THALLIUM SCINTIGRAPHY AND EXERCISE ELECTROCARDIOGRAPHY

Cardiac events subsequently occurred in two of the 104 (65·8%) patients with normal scintigraphy—that is no transient defect and a normal exercise electrocardiogram. In 35 (22·2%) patients either the exercise electrocardiogram was abnormal or thallium scintigraphy showed a transient defect. Three of these patients later suffered a cardiac event. In 19 (12·0%) patients both tests were abnormal—the exercise electrocardiogram showed ST deviation or was uninterpretable and thallium scintigraphy showed a transient defect. Five of these later suffered a cardiac event. Figure 3 shows the estimated percentage without a cardiac event over time. Patients in whom both tests were abnormal had a significantly worse prognosis.

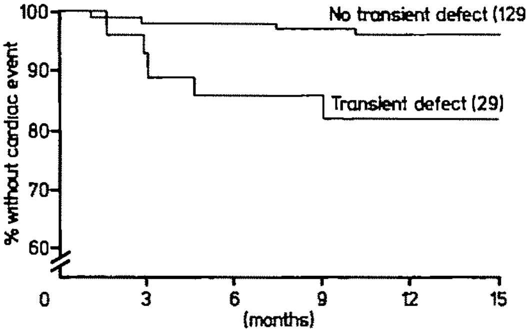

Fig 2 *Kaplan-Meier estimates of percentage without a cardiac event in patients with transient defects or without transient defects on thallium scintigraphy.*

Discussion

Patients admitted with suspected acute myocardial infarction because of chest pain in whom the diagnosis is not subsequently confirmed have a high risk of cardiac events after discharge.[1–3] In the present groups the prognosis was only slightly better in the

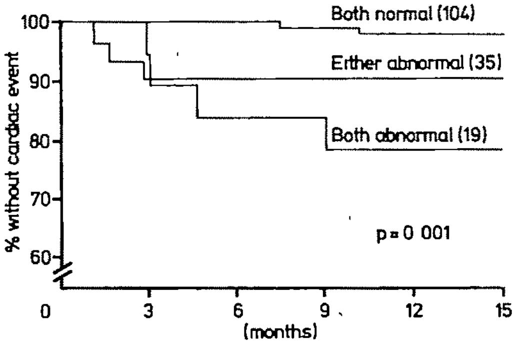

Fig 3 *Kaplan-Meier estimates of percentage without a cardiac event in relation to the combination of exercise electrocardiography and thallium scintigraphy. Abnormal exercise electrocardiography includes ST deviation or uninterpretable ST segment. Abnormal thallium scintigraphy includes transient defects only. Both normal, n = 104; either abnormal, n = 35; both abnormal, n = 19 (p = 0·001).*

257 patients without confirmed acute myocardial infarction (fig 1) than it was in a corresponding group of 275 patients discharged after confirmed acute myocardial infarction ($p = 0{\cdot}05$).[13] The estimated risk of cardiac events after one year was 8·7% and 13·9% respectively.

The purpose of this study was to see whether it was possible to identify different risk groups of patients without confirmed acute myocardial infarction by thallium scintigraphy alone or in combination with exercise electrocardiography. The presence of transient defects on thallium scintigraphy was significantly associated with later cardiac events (fig 2). Although the combination of permanent and transient defects identified eight out of 10 patients with cardiac events in the observation period, scintigraphy alone was not a specific indicator of prognosis, because permanent defects on their own were not related to prognosis.

These results accord with previous studies that have shown that thallium scintigraphy gives prognostic information on patients evaluated for chest pain.[6 7] Iskandrian *et al* showed that the number of defects, transient or permanent, and the presence of perfusion defects were the two most important independent predictors of cardiac events in such patients.[7]

Patients with chest pain and normal thallium scintigraphy have a good prognosis.[14 15] Pamelia *et al* found a cardiac event rate of 1·1% per year in such patients.[14] The present study shows almost the same results. The incidence of cardiac events after one year was only 2·2% (table 1). These results are also supported by the findings of Ilsley *et al* and Patterson *et al*, who found that in patients with chest pain important coronary artery disease can be ruled out with more than 90% certainty if both an exercise test and thallium scintigraphy are normal.[16 17]

The prognosis in patients in whom thallium scintigraphy was not possible was slightly worse than that in patients in whom it was performed. The selection of patients for scintigraphy was determined randomly by factors independent of the study. Thus the difference in prognosis must have occurred by chance.

ST segment depression during exercise was associated with an unfavourable prognosis, and a normal ST segment was associated with a good prognosis (table). This accords with studies of patients with angina pectoris.[18] The ST segment response during exercise was uninterpretable in 15% of the patients (table). These patients too had a less favourable prognosis. When patients with an uninterpretable exercise electrocardiogram were grouped with patients with ST segment depression during exercise—that is an abnormal exercise electrocardiogram—the prognostic information given by the exercise electrocardiogram and in thallium scintigraphy (table) is slightly different, and in this study thallium scintigraphy gives the best differentiation between groups.

A combination of the two methods gave the most information about prognosis (fig 3). The patients could be divided into three groups according to the event free rate after one year: (*a*) a low risk group with two normal tests, making up two thirds of the total group, where 98·8% were event free; (*b*) a high risk group with two abnormal tests, 12% of all patients, of whom 78·8% were event free; (*c*) a medium risk group, making up one fifth of the population, with one abnormal test only in whom 90·8% were event free. Differences between risk groups did not become apparent until 3–6 months after assessment.

The study design meant that we studied younger patients with chest pain and without severe disease, other than possible coronary heart disease. Nevertheless, the results show that both exercise electrocardiography and thallium scintigraphy can identify high and low risk groups. The combination of the methods adds further prognostic information. Most patients are at low risk and such patients can be reassured about the probable benign nature of their chest pain and can be discharged without the need for outpatient follow up or further investigations. Patients with a high risk should be followed closely after discharge.

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Initiation of ventricular fibrillation by supraventricular beats in patients with acute myocardial infarction

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SUMMARY The role of supraventricular extrasystoles in the initiation of ventricular arrhythmia was studied in 72 consecutive patients who developed primary ventricular fibrillation during the acute phase of myocardial infarction. In six patients (8%), a total of 12 episodes of ventricular fibrillation and 16 episodes of ventricular tachycardia were initiated by supraventricular extrasystoles. Ventricular fibrillation and tachycardia were initiated by single supraventricular extrasystoles in 16 and by salvos ≥two beats in 12 episodes. The RR coupling interval of the supraventricular impulse immediately preceding ventricular tachycardia ranged from 240 to 420 ms (mean 356 (62)) and was characteristic of R-on-T (prematurity index <1) in 63% of episodes. Average peak serum creatine kinase activity in the six patients in whom ventricular tachycardia was initiated by a supraventricular extrasystole was 1275 units compared with 720 units in the remaining 66 patients. Five of these six patients later showed evidence of pump failure. Lignocaine or procainamide or both suppressed the ventricular arrhythmia in five of the six patients.

The initiation of ventricular fibrillation or tachycardia by supraventricular extrasystoles in acute myocardial infarction is not uncommon and may reflect the increased vulnerability of the heart after a large infarct. These arrhythmias may respond to drugs that suppress ventricular irritability.

The initiation of ventricular arrhythmia by supraventricular extrasystoles is uncommon.[1 2] The initiation of ventricular fibrillation by supraventricular extrasystoles in patients with acute myocardial infarction has been rarely reported.[3 4] To assess the role of supraventricular extrasystoles in the initiation of ventricular fibrillation in patients with acute myocardial infarction we critically analysed the mode of initiation of the tachycardia in 72 consecutive patients in whom the onset of one or more episodes of ventricular fibrillation was recorded.

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Patients and methods

We studied 72 consecutive patients (61 men and 11 women, mean (SD) age 59(11)) admitted to the coronary care unit with acute myocardial infarction who developed primary ventricular fibrillation. All patients were admitted within 24 hours of the onset of chest pain, and the mean time taken to reach the coronary care unit was four hours. The diagnosis of acute myocardial infarction depended on all the following criteria being present: (*a*) a typical clinical history; (*b*) new Q waves or typical evolutionary ST-T changes; and (*c*) characteristic serial changes in the activity of serum creatine phokinase, alanine aminotransferase, and lactic dehydrogenase. The site of old and acute infarction was defined by the criteria of Lipman and Massie.[5] Primary ventricular fibrillation was defined as ventricular fibrillation in the absence of appreciable congestive failure, pulmonary oedema, and cardiogenic shock.[6 7]

In all 72 patients continuous electrocardiographic monitoring (4–108 hours per patient, mean (SD) 32 (28) hours) was performed. Each episode of non-sustained ventricular tachycardia (defined as ⩾3 extrasystoles and lasting <30 seconds at a rate of ⩾100 beats per minute), sustained ventricular tachycardia (lasting >30 seconds or requiring earlier termination because of haemodynamic compromise), and ventricular fibrillation was recorded, and the mechanism of initiation was analysed. The prematurity index of the supraventricular impulse that initiated ventricular tachycardia or ventricular fibrillation was determined by dividing its RR coupling interval by the QT interval of the basic supraventricular impulse. The basic QT interval was obtained by averaging the QT intervals of the 3–5 consecutive basic supraventricular impulses immediately preceding the one to which the supraventricular extrasystole was coupled. A prematurity index <1 was considered to represent short coupling or R-on-T phenomenon. Lignocaine infusion (1 to 4 mg/minute with an initial bolus injection of 75–100 mg) or procainamide infusion (2–6 mg/min after an initial dose of 1 mg/kg bodyweight over 10–20 minutes) or both were given to all patients who developed ventricular arrhythmia. None of these drugs was given before the onset of primary ventricular fibrillation.

Results

A total of 152 episodes of primary ventricular fibrillation were recorded in the 72 patients. Twelve episodes (8%) in six (8%) patients were initiated by supraventricular impulses. In addition, eight runs of non-sustained ventricular tachycardia and eight episodes of sustained ventricular tachycardia were also initiated by supraventricular impulses in the same six patients. None of the patients had evidence of accessory atrioventricular pathways. The basic heart rate preceding the onset of ventricular arrhythmia in the six patients was not significantly different from that of the rest of the group. The frequency of supraventricular extrasystoles in these six patients and the remaining patients could not be compared because data were not available for all 66. Nevertheless, paroxysmal supraventricular arrhythmias (supraventricular tachycardia and atrial flutter and fibrillation) occurred in three (50%) of the six patients and in 15% of the rest of the group.

Table 1 summarises the clinical data in the six patients. Five patients had acute anterior wall myocardial infarction. Two patients developed right bundle branch block and left anterior hemiblock and a third patient developed isolated left anterior hemiblock. A mean peak serum creatine kinase activity of 1275 U/l (compared with 729 U/l in the remaining 66 patients) and an adverse clinical outcome suggested extensive myocardial damage in these six patients. Five of the six patients developed congestive heart failure, two patients died during initial hospital stay from pump failure, and a third patient died after a prolonged complicated course after rupture of the interventricular septum. All the episodes of ventricular fibrillation that we analysed occurred in the absence of pronounced congestive failure, pulmonary oedema, and cardiogenic shock and thus conformed to the criteria of primary ventricular fibrillation. One patient was admitted with a clinical picture consistent with intermittent coronary artery spasm and went on to develop extensive anterior wall myocardial infarction within 24 hours. Three episodes of non-sustained ventricular tachycardia and one episode of ventricular fibrillation initiated by supraventricular extrasystoles occurred during periods of ST elevation associated with ST-T alternans (fig 1).

Table 2 summarises the mode of initiation of 12 episodes of primary ventricular fibrillation and 16 episodes of non-sustained or sustained ventricular tachycardia by supraventricular impulses. The tachycardia was initiated by a single supraventricular extrasystole in 16 episodes, by two supraventricular extrasystoles in nine episodes, and by ⩾3 extrasystoles in three. The QRS complex of

Table 1 *Clinical data in six patients with primary ventricular fibrillation initiated by supraventricular extrasystoles*

Case	*Site of infarction*	*Peak CK*	*BBB*	*Follow up*
1	Anterior	1725	RBBB + LAH	Patient died from late pump failure
2	Anterior	1275		Discharged from hospital
3	Anterior	1215	RBBB + LAH	Patient died from late pump failure
4	Anterior + old inferior	1425	LAH	Patient developed VSD and later died from pump failure
5	Anterior	900		Discharged from hospital
6	Inferior + old anterior	740		Discharged from hospital

CK, serum creatine kinase, BBB, bundle branch block, RBBB, right bundle branch block, LAH, left anterior hemiblock; VSD, ventricular septal defect

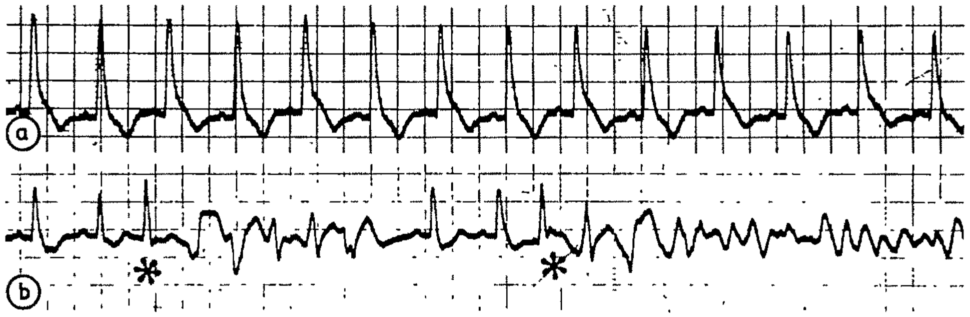

Fig 1 *Electrocardiogram showing non-sustained ventricular tachycardia and ventricular fibrillation initiated by supraventricular extrasystoles (asterisks) in a patient with Prinzmetal angina associated with ST-T alternans. Extensive anterior wall myocardial infarction developed within 24 hours of onset of symptoms.*

the supraventricular extrasystole initiating ventricular arrhythmia was similar to the QRS complex of the basic supraventricular rhythm. In the 16 episodes in which the tachycardia was initiated by a single supraventricular extrasystole the RR coupling interval of the extrasystole ranged from 240 to 420 ms (mean (SD) 356 (62) ms) and had a prematurity index <1 (R-on-T phenomenon) in 10 (63%) of 16 episodes. There was no significant difference between the prematurity index of the supraventricular impulse that initiated an episode of ventricular tachycardia or ventricular fibrillation in the same patient. In some patients the coupling interval of the supraventricular extrasystole initiating non-sustained ventricular tachycardia was shorter than the one initiating ventricular fibrillation (fig 2), while in other patients the reverse was true. There was also no significant difference in the basic heart rate preceding the onset of either type of tachycardia in the same patient. In five of the six patients at least one episode of ventricular tachycardia or ventricular fibrillation was also initiated by ventricular extrasystoles. The coupling interval of the ventricular extrasystole that initiated the tachycardia was not significantly different from the RR interval of the supraventricular extrasystole that induced the arrhythmia in the same patient. In the remaining patient all episodes of ventricular arrhythmia were initiated by supraventricular impulses (fig 3). Panels a and b of fig 3 show two episodes of sustained ventricular tachycardia each initiated by a single supraventricular extrasystole. Panel c shows the onset of ventricular fibrillation after two closely coupled supraventricular extrasystoles, while panel d shows ventricular fibrillation after an episode of supraventricular tachycardia.

All episodes of ventricular fibrillation and some episodes of ventricular tachycardia required cardioversion. In the six patients in whom ventricular arrhythmia was initiated by supraventricular extrasystoles, the arrhythmia was suppressed by lignocaine in two patients. The frequency of supraventricular extrasystoles before and after suppression of the ventricular arrhythmia was evaluated in those two patients and showed no appreciable change. After lignocaine or procainamide or both, ventricular fibrillation did not recur in three other patients but non-sustained ventricular tachycardia was only partially suppressed. In the sixth patient bretylium infusion and overdrive ventricular pacing were required to suppress the tachycardia.

Discussion

The present report shows that initiation of primary ventricular fibrillation by supraventricular extrasystoles in acute myocardial infarction is uncommon but by no means rare. We use the term supraventricular extrasystoles rather than atrial extrasystoles because, in the absence of intracardiac

Table 2 *Mode of initiation of ventricular arrhythmias by supraventricular impulses*

	Number of episodes		
Mode of initiation	*NSVT*	*SVT*	*VF*
Single SVES	5	3	8
Two SVES	3	3	3
SVT	0	2	1
Total	8	8	12

NSVT, non-sustained ventricular tachycardia; SVT, sustained ventricular tachycardia; VF, ventricular fibrillation; SVES, supraventricular extrasystole; SVT, supraventricular tachycardia defined as ≥3 at the rate of ≥100 beats/min

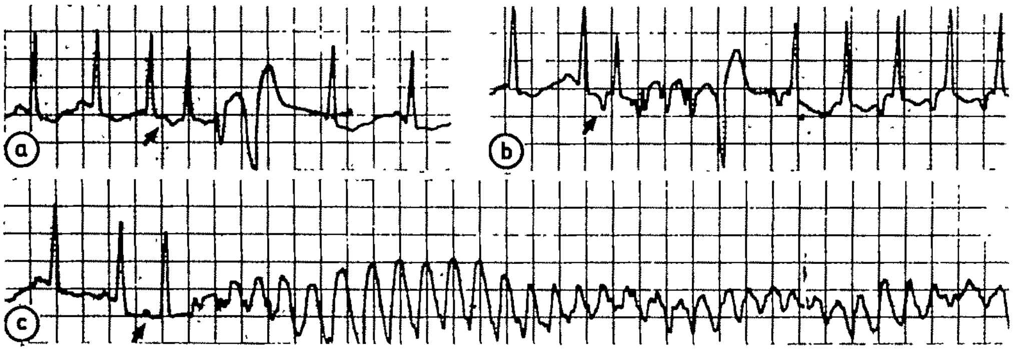

Fig 2 *Electrocardiograms showing supraventricular extrasystoles (arrows) initiating ventricular couplets (a), non-sustained ventricular tachycardia (b), and ventricular fibrillation (c) in a patient with acute myocardial infarction.*

recordings, atrioventricular junctional beats could not be excluded. In 8% of the patients who developed primary ventricular fibrillation and in 8% of the episodes of ventricular fibrillation, the arrhythmia was initiated by supraventricular impulses. In those patients, several episodes of non-sustained or sustained ventricular tachycardia were also initiated by supraventricular impulses. The prematurity index of the supraventricular QRS complex initiating 63% of the episodes of ventricular tachycardia was < 1, and was thus characteristic of an R-on-T phenomenon. This was explained by an

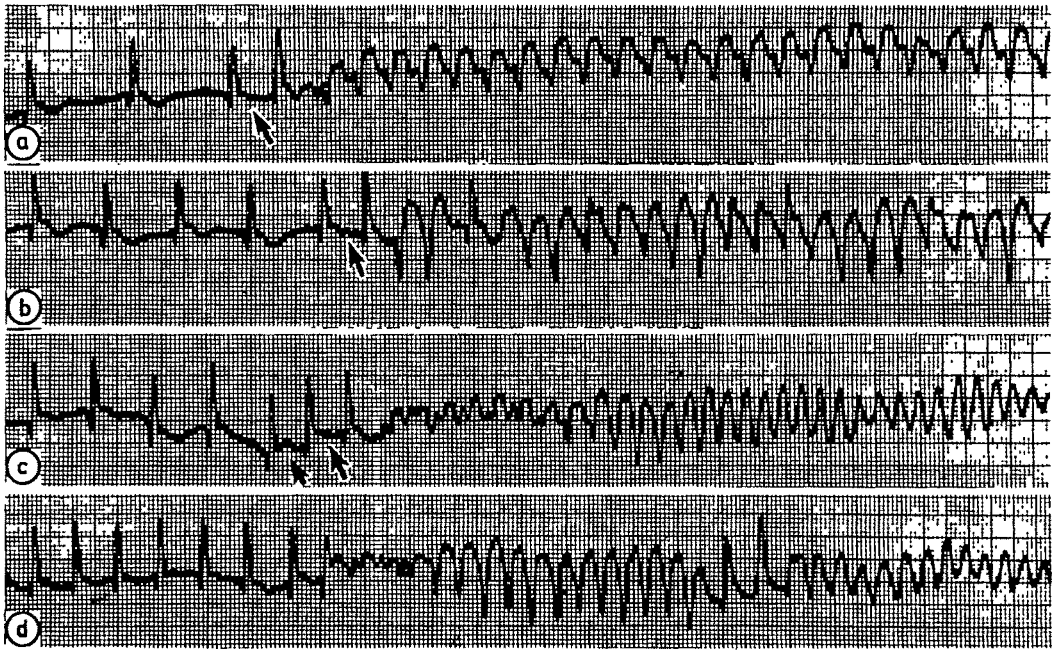

Fig 3 *Electrocardiograms obtained from a patient with acute myocardial infarction showing (a) the initiation of uniform ventricular tachycardia by a supraventricular extrasystole, (b) the initiation of multiform ventricular tachycardia by a supraventricular extrasystole, (c) the initiation of ventricular fibrillation by two supraventricular extrasystoles, and (d) the initiation of ventricular fibrillation after supraventricular tachycardia. Supraventricular extrasystoles are indicated by arrows.*

early coupling of the premature P wave to the preceding QRS complex in the presence of a normal or only slightly prolonged PR interval. This may suggest a certain degree of enhanced atrioventricular conduction in some of those patients probably secondary to increased catecholamine concentrations. In the remaining 37% of episodes, however, the coupling interval of the supraventricular QRS complex that initiated the arrhythmia was long. This is not significantly different from the previously reported frequency of 41% of episodes of primary ventricular fibrillation initiated by ventricular extrasystoles with a prematurity index of > 1.[3] Also there was no significant difference in the heart rate preceding arrhythmias initiated by ventricular or supraventricular extrasystoles. The only recognisable difference between the small group of patients in whom primary ventricular fibrillation was initiated by supraventricular extrasystoles and the larger group in whom the arrhythmia was prompted by ventricular extrasystoles was that the former group seemed to have a larger infarct and more extensive myocardial damage. This was evident from a higher peak creatine kinase activity and a more complicated course, with congestive heart failure in five of the six patients and death from terminal pump failure in three of them. It is reasonable to speculate that the more extensive myocardial ischaemia may have increased ventricular vulnerability.

Under experimental conditions it is not uncommon to induce ventricular fibrillation by supraventricular extrasystoles if these are properly timed and if ventricular vulnerability is sufficiently altered. For example, ventricular fibrillation was induced by supraventricular extrasystoles in infant goats and pigs because earlier coupling could be achieved since in these animals the refractory period of the atrioventricular conduction system is shorter than that of the ventricle.[8] On the other hand, very early coupling of supraventricular beats is not required to induce ventricular fibrillation if ventricular vulnerability is altered by experimental acute ischaemia,[9] subacute ischaemia,[10] or hypothermia.[11] These interventions can lengthen the refractory period, and if combined with a critical degree of spatial nonuniform distribution (characterised by adjacent regions of short and long refractoriness) could create "ventricular vulnerability"—in other words, the necessary electrophysiological conditions for extrasystoles to initiate reentrant excitation.[12]

The concept of ventricular vulnerability was first described in animal models by Wiggers and Wegria who showed that ventricular arrhythmias could be induced by a single test stimulus applied during the relative refractory period.[13] This work introduced the concept of a triggering mechanism—(that is the critically coupled extrasystole) and an appropriate electrophysiological precondition (that is nonuniform refractoriness during the vulnerable period), setting the stage for reentrant excitation. Later the clinical expression of this concept was highlighted by the phrase "R-on-T phenomenon".[14 15] There are at least two limitations to extrapolating from these initial experimental observations to spontaneous ventricular arrhythmias in the clinical setting. First, although in the normal heart the vulnerable period is limited to the QT interval, ischaemia can extend the vulnerable phase throughout a major portion of the diastolic interval,[10] so that ventricular arrhythmias caused by reentry could be initiated by a ventricular extrasystole falling outside the QT interval. The present study shows that the same is true when the triggering mechanism of the ventricular arrhythmia is a supraventricular extrasystole. Secondly, the concept of a triggering stimulus and an appropriate electrophysiological basis for arrhythmia can only be applied to the situation when the ventricular arrhythmia is induced in the electrophysiological laboratory by critically coupled ventricular or supraventricular electrical stimuli, and when, as in the present study, the arrhythmia is initiated by spontaneous supraventricular extrasystoles. On the other hand, when a spontaneous ventricular arrhythmia is triggered by a ventricular extrasystole two different mechanisms could be invoked. One, that the first ventricular extrasystole represents the discharge of an automatic focus that triggers a subsequent arrhythmia based on reentry. The other possibility is that both the initiating and subsequent impulses are part and parcel of the same electrophysiological mechanism of reentrant excitation. The two electrophysiological mechanisms have been clearly demonstrated in the canine post-infarction model[16] but cannot be discerned in the clinical setting. In at least two of our six patients the ventricular arrhythmia was apparently suppressed by drugs that may have altered the underlying electrophysiological conditions for reentry without affecting the supraventricular triggering mechanism.

We conclude that initiation of ventricular fibrillation by supraventricular extrasystoles in acute myocardial infarction is not uncommon. The presence of extensive myocardial injury may result in a greater degree of altered ventricular vulnerability and provides the necessary electrophysiological basis for the initiation of the ventricular arrhythmia by supraventricular extrasystoles. These arrhythmias may respond to drugs that suppress ventricular irritability without affecting the supraventricular triggering mechanism.

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Coronary thrombosis and platelet/fibrin microemboli in death associated with acute myocardial infarction

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SUMMARY The frequency and clinical significance of platelet/fibrin microemboli in the microcirculation were investigated in 24 patients whose deaths (before and during hospital admission) were associated with acute myocardial infarction. An acute coronary thrombus was present in all the hearts. In nine hearts an acute thrombus was found in more than one major epicardial coronary artery. A total of 35 acute thrombi were found in the 24 hearts. Platelet/fibrin microemboli were found in 19 (79%) hearts. Eighteen patients died in hospital. The hearts of 16 of these cases showed microemboli; 16 had important arrhythmias or various forms of heart block; 13 showed acute pathological changes in the conduction system. Fourteen of the deaths in hospital were primarily the result of cardiogenic shock and four were primarily caused by arrhythmia. Six of the deaths that occurred before admission to hospital were regarded as being arrhythmic in origin. Three of these showed microemboli and the other three had acute pathological changes in the conduction system. Microemboli were found in two (24%) of 12 control hearts.

Coronary thrombosis was found in most deaths caused by acute myocardial infarction and platelet/fibrin microemboli were present in the majority of such hearts. These may arise from the coronary thrombus in the larger upstream vessel supplying the microcirculation.

Myocardial infarction is caused by or is closely associated with acute coronary thrombosis. Recent studies show that the frequency of occlusion in acute myocardial infarction decreases during the first 24 hours of a transmural infarction.[1] These data suggest that lysis of thrombi and even of occlusions may occur in the course of acute infarction and may convert an occlusion into a non-occlusive thrombus. The exposed surface of a non-occlusive thrombus is often covered with friable, loosely attached platelet/fibrin aggregates.[2] Some of these fragments undoubtedly pass distally to the microcirculation.[3 4] The clinical significance of these microemboli has not been fully determined, but they have been reported in association with lethal rhythm disturbances, particularly ventricular arrhythmias, myocardial infarction, and sudden cardiac death.[5-7] This report will show that many patients who die of acute myocardial infarction not only have acute coronary thrombosis, but also have platelet/fibrin microemboli in the microcirculation, commonly distal to an acute coronary thrombus. In addition, most of these patients have important arrhythmias, and they often have acute pathological changes in the conduction system.

Patients and methods

The hearts of 24 patients (17 men and seven women, aged 32–93 (mean 59)) who died of a microscopically confirmed acute myocardial infarction were subjected to a detailed pathological study of the coronary arteries, conduction system, and myocardium. Six patients died suddenly out of hospital and their hearts were obtained from the Sacramento County coroner's office. No electrocardiographic data were available for these six patients, and their deaths are assumed to have been caused by arrhythmia. None

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of them had evidence of myocardial rupture or congestive changes in the lungs. Eighteen patients died after admission to the hospital and for all of them we had monitor strips or electrocardiograms showing the presence or absence of arrhythmias. Thirteen patients had been given anticoagulants, heparin, or warfarin.

Hearts were selected on the basis of (*a*) microscopic evidence of acute myocardial infarction; (*b*) satisfactory injection of the coronary arteries with a barium gelatin mass; (*c*) absence of previous heart operation, coronary angioplasty, or streptokinase. No patients meeting these criteria were excluded. The cause of death in 14 hospital patients was cardiogenic shock; a lethal arrhythmia, confirmed electrocardiographically had caused the deaths of the other four hospital patients. The infarctions were classified as transmural (full thickness of the ventricular wall) or non-transmural.

We used a postmortem, angiographic, photographic technique with a coloured barium gelatin mass to study the hearts.[2] Briefly, hearts were obtained fresh and uncut at the necropsy table, the coronary arteries were cannulated, and injected with a coloured barium gelatin mass. All hearts were injected within 24 hours of death.

After fixation in formalin, the entire length of all major epicardial coronary arteries was dissected from the heart and decalcified. *X* rays were taken of the dissected coronary arteries before and after decalcification. Figure 1 shows a typical barium filled coronary artery. Arteries were then cut every 2–3 mm, embedded in paraffin and sectioned at 6 μm. These coronary artery sections were stained with haematoxylin eosin and also with Martius scarlet blue stain to detect fresh fibrin. Ten or more blocks of myocardium were taken from standardised sites and any suspected areas of infarction. Blocks of tissue containing the sinus and atrioventricular nodes, His bundle, and proximal bundle branches were removed and embedded for histological study. All sections of myocardium, atrioventricular node, and sinus node were stained with haematoxylin eosin and Martius scarlet blue. All microscopical sections were thoroughly searched for platelet/fibrin microemboli. The colouring material used in the injection mass identified the myocardial distribution of a given coronary artery. Thus fragments found in the distribution of a given coronary artery were assumed to have originated in or to have passed down through this artery.

An acute coronary thrombus in the main epicardial arteries was defined as an attached, organised mass of fibrin and platelets that stained appropriately with the Martius scarlet blue stain. Platelet/fibrin microemboli were identified microscopically as organised groups of platelets and fibrin, with clearly identifiable fibrin strands, present in a small myocardial arteriole. Platelet aggregates without fibrin were not counted in this study. Postmortem fibrin was distinguished as a looser, more filamentous structure, with no organisation of the fibrin.

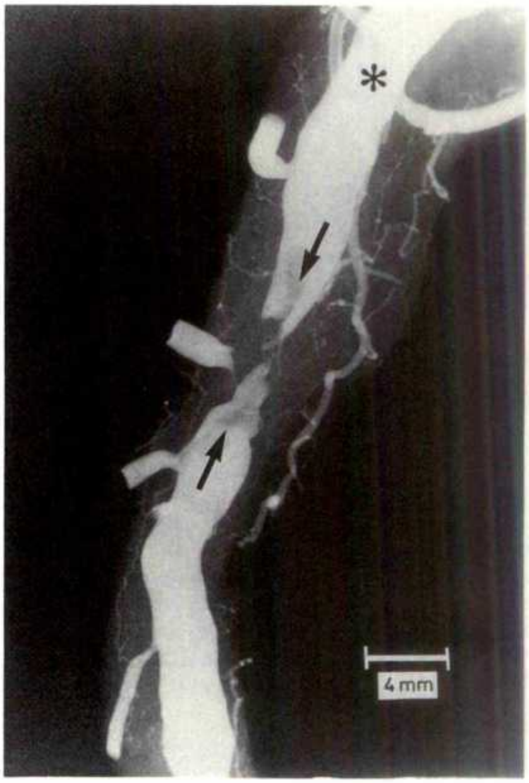

Fig 1 *x ray taken of an epicardial right coronary artery after decalcification. Asterisk indicates area close to coronary ostium and arrows show the site of filling defects proximal and distal to the obstruction, which was confirmed to be an acute thrombus.*

CONTROL PATIENTS

The hearts from 12 men (aged 19–81, mean 36) were examined to determine the frequency of microemboli in patients whose deaths were caused by noncardiac disease, accidents, or violence (n = 10) and also those whose deaths were cardiogenic but noncoronary in origin (n = 2; myocarditis, hypertrophic subaortic stenosis). Of the 10 patients dying of noncardiac disease, accidents, or violence, six hearts were injected in a manner identical to that described above and four were processed and examined without the use of injection material. The two cardiogenic control hearts were injected with the barium gelatin mass. All control hearts were prepared within 24 hours of death. Three patients, all of whom had died of non-cardiogenic causes, died within six days of admission to the hospital. The remainder were all out-of-hospital deaths.

Results

The table shows the pathological findings in all 24 cases, subdivided according to transmural or non-transmural infarction. The term "global infarction" indicates that acute infarction was found throughout the myocardium. An acute coronary thrombus was found in all the hearts. These thrombi were firmly attached to the arterial wall and had irregular surfaces with many loosely attached fragments. In nine hearts an acute coronary thrombus was found in more than one epicardial coronary artery. In the 24 patients, 35 acute coronary thrombi were found in separate major epicardial coronary arteries. The infarction was distal to an acute thrombus in each heart, with the exception of those with global infarction. Microemboli were present in 19 (79%) of all hearts, and most were found in the distribution of an artery that contained an acute thrombus. Figure 2 shows the appearance of a typical microembolus. Microemboli were also found in three patients with left ventricular mural thrombi. In two of these patients, microemboli were found in the distribution of an artery that did not contain an acute coronary thrombus.

Although all hearts contained a coronary thrombus, emboli were more common in patients with transmural infarction than in patients with non-transmural infarction. The difference, however, was not significant ($p > 0{\cdot}10$). Five of the six patients with non-transmural infarction died outside hospital: three had microemboli, and four had pathological changes in the conduction system.

Eighteen deaths occurred after admission to the hospital. All died within 17 days of admission; eight within the first 48 hours. There were significant arrhythmias, over and above single atrial or ventricular unifocal extrasystoles in 16 patients; five of these also developed various forms of new onset heart block. The forms of heart block included 2:1 block, right bundle branch block, left bundle branch block, atrioventricular dissociation, and junctional rhythm. There was ventricular tachycardia or ventricular fibrillation (other than as an agonal rhythm) in 12 (60%) patients. Two patients did not show any type of arrhythmia. The conduction system was

Table *Site of thrombus in relation to location of infarction and distal microemboli in patients with transmural and non-transmural infarction*

Patient	*Site of acute thrombosis*			*Site of infarct location*	*Site of microemboli*	*Anticoagulants given*
				Transmural infarction		
1	LAD			Ant	None	No
2			RC	Inf	Inf/Lat	Yes
3	LAD			Ant	Ant	Yes
4	LAD,		RC	Inf	Ant/Inf/Avn	Yes
5	LAD			Ant	Ant/Inf	Yes
6	LAD			Ant	Ant	No
7	LAD			Global	Ant/Inf/Lat	No
8	LAD,	Circ,	RC	Global	Ant/Inf	No
9	LAD,	Circ,	RC	Global	Ant/Lat	No
10	LAD			Ant	Ant/Lat	Yes
11	LAD			Ant	None	Yes
12			RC	Inf	Inf/Sep/Lat	Yes
13	LAD,		RC	Inf	Ant/Inf/Sep	Yes
14	LAD			Ant	Ant/Sep/Inf	Yes
15	LAD,		RC	Global	Ant/Inf	Yes
16		Circ,	RC	Inf	Inf	Yes
17	LAD		RC	Ant/Lat	Ant/Inf/HB	Yes
18	LAD			Global	Ant/Lat	Yes
Subtotal	15	3	9		16	
				Non-transmural infarction		
19	LAD		RC	Inf	None	No
20	LAD			Ant	Septal	No
21	LAD			Ant/Inf	None	No
22	LAD		RC	Inf	None	No
23			RC	Inf	Inf	No
24	LAD			Septal	Inf/Lat	No
Subtotal	5		3		3	
Total	20	3	12		19 (79%)	

LAD, left anterior descending coronary artery; RC, right coronary artery; Circ, circumflex coronary artery; Ant, anterior; Lat, lateral; Global, infarction found diffusely throughout the myocardium; Inf, inferior; Sep, septal; Avn, atrioventricular node; HB, His bundle.

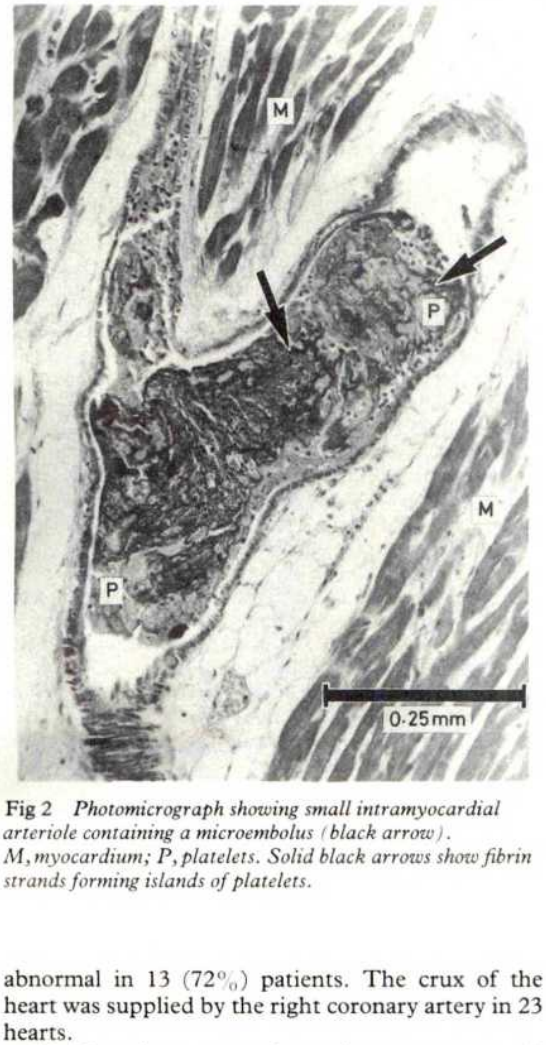

Fig 2 *Photomicrograph showing small intramyocardial arteriole containing a microembolus (black arrow). M, myocardium; P, platelets. Solid black arrows show fibrin strands forming islands of platelets.*

abnormal in 13 (72%) patients. The crux of the heart was supplied by the right coronary artery in 23 hearts.

Of 13 patients on anticoagulant treatment, 11 were considered to be fully anticoagulated, and of these, 10 showed microemboli.

CONTROL STUDIES

Coronary thrombosis was not found in any of the control hearts and there was no evidence of coronary disease in any of them. Two patients showed a single, but well defined, platelet/fibrin microembolus in the myocardial microcirculation. These two patients had been admitted to hospital for three and six days before death, both had severe intracranial haemorrhage, and both hearts were injected with the barium gelatin mass. No microemboli were found in any of the other control patients, whether or not they had been injected with the barium gelatin mass. This indicates that the use of the injection mass does not affect the detectability of the microemboli. The conduction system was examined in all control hearts and no acute changes were found.

Discussion

PLATELET/FIBRIN MICROEMBOLI IN THE MICROCIRCULATION

We found platelet/fibrin microemboli in most patients who died of acute myocardial infarction, especially of transmural infarction. We found that the more comprehensive the search for microemboli, the more we found. There are three possible sources of the platelet/fibrin microemboli and these are not necessarily mutually exclusive. First, the formation of microemboli may be an agonal event or may occur soon after death. Platelet aggregation during acute illness has been reported[8]; for this reason, pure platelet aggregations were not counted in this study. The fragments we considered to have been formed before death were tightly knit, compact, well-formed fragments of fibrin, with or without platelets (fig 2), unlike the loose, unorganised appearance of postmortem fibrin.

A second possibility is that microemboli may occur as a result of increased platelet reactivity, which is sometimes seen in patients with acute myocardial infarction.[9] The condition is, as yet, poorly defined, and there are no pathological studies for comparison. Except in the two cases of intracranial haemorrhage, however, microemboli were only found in association with a thrombus. Thus it is unlikely that they represent a primary event.

The third possibility is that the microemboli may originate from an acute coronary thrombus located in the upstream coronary artery. Most microemboli in this study were distal to a coronary thrombus, which could have served as a source for these fragments. In addition, those patients with ventricular mural thrombi had microemboli in the microcirculation in the distribution of an artery that did not contain a thrombus. Furthermore, in a previous study of coronary thrombosis and sudden death,[2] platelet/fibrin microemboli were found in most cases. The thrombi in this and the current study were characterised by their irregular surface and loosely attached fragments. Clearly, the thrombus is in a dynamic state of change undergoing episodic formation and dissolution as a result of the flow of blood, platelet disaggregation, and fibrinolysis.[1 4 10] The body of evidence thus supports the notion that platelet/fibrin microemboli originate from a proximal thrombus.

Microemboli were found in the microcirculation irrespective of the length of hospital stay. But neither the time of embolisation nor the state of the fibrinolytic system at the time of death were known. None the less, as all patients died as a result of a myocardial infarction and the majority of the patients had microemboli, it is possible that platelet/fibrin microemboli contributed to the haemodynamic and/or electical instability in these patients. The present data show that such embolisation is a possibility irrespective of the age of the infarction.

Anticoagulation seemed to have little effect on the presence or absence of microemboli. The effectiveness, therefore, of anticoagulants to retard the thrombotic process and reduce the frequency of microemboli is questionable.

CLINICAL MANIFESTATIONS OF MICROEMBOLI

An important question is the relation between microemboli and death associated with acute myocardial infarction. Numerous investigators have provided evidence that microemboli may be involved in focal fibrosis,[11] subendocardial injury,[12] unstable angina pectoris,[13] and sudden cardiac death.[2 6 7] To our knowledge, however, no correlation between microemboli and death associated with acute myocardial infarction has yet been made. The present finding of a high frequency of microemboli indicates that the two might be related. The above evidence also suggests that microemboli do have pathogenetic potential and that they are apparently capable of causing various clinical symptoms.

The relation between microemboli and arrhythmias is not clear. Important arrhythmias or recent onset heart block, assuming that all out-of-hospital deaths were arrhythmic in origin, were present in 92% of patients in this study. Microemboli were found in 79%. Most (61%) arrhythmias were ventricular in origin. Conduction system abnormality was also present in 61% of cases. The occurrence of arrhythmias, therefore, correlated reasonably well with the presence of microemboli, as well as with some types of conduction system abnormalities. The pathological findings, however, could not be correlated with specific arrhythmias. In several cases microemboli were found in or immediately adjacent to the conduction system. This evidence does not prove that microemboli caused the arrhythmias or heart block, but neither does it rule out that possibility. At the very least microemboli should be considered a possible mechanism for producing transient, severe, reversible ischaemia of focal areas of the myocardium and/or the conduction system.

In summary, platelet/fibrin microemboli in the microcirculation are common in patients dying of acute myocardial infarction and they seem to be derived from a proximal thrombus. Arrhythmias and acute pathological changes in the conduction system are also common in these cases; whether or not the arrhythmias are related to platelet/fibrin microemboli is unknown and requires further study.

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Prevalence of ischaemic heart disease: the Caerphilly and Speedwell surveys

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SUMMARY Mortality from ischaemic heart disease remains high in the United Kingdom, and the present report describes the prevalence of the various epidemiological manifestations of the disease in two recent community studies with a common core protocol, each containing samples of over 2000 men, carried out in South Wales (Caerphilly) and the West of England (Speedwell, Bristol). The prevalence of electrocardiographic evidence of ischaemia was similar in the two communities—8·7% of men aged 45–49 years rising to 18·6% in men aged 55–59 years in the samples from South Wales, and 8·0% and 17·2% respectively in the Bristol population. The overall prevalence of angina was 7·7% in Caerphilly and 7·8% in Speedwell in men aged 45–59 years, but symptoms of severe chest pain were more commonly reported in South Wales than in Speedwell (10·1% compared with 6·3%). The data, however, suggested that the overall prevalence of ischaemic heart disease was very similar in the two areas. The prevalence of ischaemic heart disease was compared with that found in other population studies carried out in the United Kingdom and was higher than that found when employed men only were studied. There were substantial differences in mortality between the two areas; possible reasons for this are differences in community or medical services, smoking habit, or unemployment rates.

Any recent decline in mortality from ischaemic heart disease in the United Kingdom has been modest compared with that experienced by the United States and some other western countries.[1] A few British studies carried out between 1968 and 1980 have described the prevalence of ischaemic heart disease in working populations[2 3] and in the general population.[4] We describe the prevalence of the various manifestations of ischaemic heart disease—history of possible myocardial infarction, angina, and electrocardiographic evidence of ischaemia—in two recent community studies with a common core protocol. These prevalence figures were compared with those found in the other British studies.

Patients and methods

Study populations—In Caerphilly and five outlying villages a total sample of middle aged men was selected. The men were chosen by date of birth and when they were seen they were aged 45 to 59 years inclusive. In Speedwell a total sample of men from the age-sex registers of 16 general practitioners working from two health centres in east Bristol was chosen. These men were aged between 45 and 59 inclusive on 1 September 1978, just before the start of the study. In both areas the recruitment phase of the study took between three and four years. Thus the men in the Speedwell study were aged between 45 and 63 years when they were seen.

Survey methods—In Caerphilly a total of 2818 men were eligible for inclusion and were invited to attend one of several local clinics for a cardiovascular examination. In the Bristol population 2550 men were eligible for inclusion in the study and were invited by a letter from their own general prac-

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titioner to attend a single local centre, the Speedwell clinic.

At the clinics in both areas the London School of Hygiene and Tropical Medicine chest pain questionnaire[5] was administered to all men and a 12 lead electrocardiogram was taken. The electrocardiograms were Minnesota coded and checked[5] by two experienced observers common to both studies. In both areas a series of other questionnaires was completed and measurements were made. These included details of medical history, smoking habit, occupation (for coding of social class), and family history of ischaemic heart disease. In Caerphilly a record was made of whether the man was currently employed, unemployed, or retired. In both areas height without shoes was measured with a Holtain stadiometer, and the men were weighed on a beam balance. All instruments were checked before each clinic throughout the study.

Definitions of ischaemic heart disease—Angina was defined from the London School of Hygiene and Tropical Medicine chest pain questionnaire in the standard manner as grade 1 (chest pain only on walking uphill or hurrying) and grade 2 (chest pain on walking at an ordinary pace on the level). A past history of possible myocardial infarction was defined from the same questionnaire as a positive answer to the question "Have you ever had a severe pain across the front of your chest lasting for half an hour or more?"

Two categories of electrocardiographic ischaemia were defined: probable electrocardiographic ischaemia was defined by Minnesota codes 1.1 and 1.2 (major and moderate Q waves) and possible electrocardiographic evidence of ischaemia 1.3 (minor Q waves), 4.1 to 4.4 (S–T wave changes), 5.1 to 5.3 (T wave inversions), and 7.1 (left bundle branch block). This classification was used by the Whitehall study.[2]

In addition, a combined category of "any ischaemic heart disease" was used. This was defined as the presence of any one or more of the following: angina (grades 1 or 2), a past history of possible myocardial infarction, or possible or probable electrocardiographic evidence of ischaemia.

Results

In Caerphilly 2512 men were examined (89% of those eligible). In Speedwell 2348 men were seen (92% of those eligible).

Table 1 shows the ages of the men in the two areas. The mean age of the men in Speedwell was two years more than that of the Caerphilly men. This is because the Speedwell sample was defined by age at a single date (1 September 1978) and the Caerphilly sample was defined by age at date of examination. In Speedwell only there were men who were aged more than 60 years when seen at the clinic. Also in Speedwell there are fewer men in the youngest age group and those are, on average, slightly older than the corresponding men in Caerphilly. The 50–59 year age groups are similar in both areas.

Table 1 *Age of the men in the two areas*

Area	*Age* 45–49	50–54	55–59	60–63	*Total*
Caerphilly.					
Number of men	828	811	873	—	2512
Mean age (yr)	47 4	52 6	57 6	—	52 6
Speedwell·					
Number of men	449	727	854	318	2348
Mean age (yr)	48 3	52 5	57 6	61 1	54 7

Table 2 gives the age specific prevalence of angina. Prevalence of both grade 1 (uphill effort only) and grade 2 (on level ground) angina increased with age in both areas. The age specific prevalence of both grade 1 and grade 2 angina was very similar in the two areas. In both areas nearly 30% of men with angina had the more severe (grade 2) angina.

Table 3 shows the prevalence of a history of severe chest pain (possible myocardial infarction). Prevalence increased with age in both areas, but was much higher in Caerphilly than in Speedwell. Overall, 253 (10·1%) men in Caerphilly have had a possible myocardial infarction compared with 163 (6·9%) men in Speedwell. After allowing for age, this difference is highly statistically significant (χ^2 (1 df) = 22·7; $p < 0·001$). This difference in prevalence was present in every age group.

Table 4 shows the prevalence figures for electrocardiographic evidence of ischaemia. Again prevalence increased with age and was similar in the two areas for each age group. There was a slight excess of all electrocardiographic evidence of ischaemia in Caerphilly at each age, but this area difference is not statistically significant (χ^2 (1 df) = 2 1; $0·05 < p < 0·10$). In both areas almost 4% of subjects have major or moderate Q waves (Minnesota Codes 1.1 and 1.2).

Men with one or more of the earlier categories of ischaemic heart disease were combined into the category "any ischaemic heart disease" and table 5 gives the age specific prevalence. One quarter (25·1%) of the men in Caerphilly had some evidence of ischaemic heart disease. In Speedwell the overall prevalence was 23·0%. In fact this underestimates the difference between the two areas because the Speedwell population is slightly older than that in Caerphilly. If the Speedwell prevalence is adjusted to the Caerphilly age structure by direct standard-

Table 2 *Number (%) of men (and prevalence of angina) by age and angina category*

Area	*Age* 45–49	50–54	55–59	60–63	*Total*
Caerphilly.					
Grade 1 angina	35 (4·2)	46 (5·7)	60 (6·9)	—	141 (5·6)
Grade 2 angina	10 (1·2)	16 (2·0)	25 (2·9)	—	51 (2·0)
Any angina	45 (5·4)	62 (7·6)	85 (9·7)	—	192 (7·6)
Total number of men	828	811	873	—	2512
Speedwell.					
Grade 1 angina	16 (3·6)	46 (6·3)	50 (5·9)	34 (10·7)	146 (6·2)
Grade 2 angina	8 (1·8)	12 (1·7)	28 (3·3)	13 (4·1)	61 (2·6)
Any angina	24 (5·3)	58 (8·0)	78 (9·1)	47 (14·8)	207 (8·8)
Total number of men	449	727	853*	318	2347*

*Angina category unknown in one man.

isation, then the overall Speedwell prevalence is 20·5%. Table 5 shows that a difference of this magnitude was found in each five year age group.

Table 6 gives the prevalence of each of the possible combinations of the three different categories of ischaemic heart disease for men aged 45 to 59 years. In general, the prevalences were very similar in the two areas. The exception to this was the percentage of men who had a history of severe chest pain (possible myocardial infarction) without either angina or electrocardiographic evidence of ischaemia (5·6% in Caerphilly compared with 2·6% in Speedwell). Clearly this is the main reason for the difference in the overall prevalence of any ischaemic heart disease between the areas.

Table 7 compares the prevalence of the various types of ischaemic heart disease in the two areas with that found in three other major British studies.

The Whitehall Study was based on 18 403 male civil servants aged 40–64 years working in government departments in London.[2] The men were examined between 1967 and 1969. Identical questionnaires were used in the present studies but the electrocardiograms, which were Minnesota coded, used the six limb leads only.

The United Kingdom Heart Disease Prevention Project studied 18 210 men aged 40–59 years employed in 24 industrial groups working mainly in factories in England and Wales.[3] The men were examined between 1971 and 1973; questionnaires were those used in the Whitehall Study and a six lead electrocardiogram was Minnesota coded.

The Regional Heart Study was based on a sample of 7735 men aged 40–59 years drawn at random from general practices in 24 British towns representative of a wide range of cardiovascular mortality in England, Wales, and Scotland.[4] Men were examined during 1978–80; questionnaires were based on those used in the Whitehall Study but the electrocardiogram used was based on three orthogonal leads. This system is suitable for computerised analysis and provides a sensitive measure of the extent of ST and T wave changes in clinical ischaemia.[6]

Both the Caerphilly and Speedwell studies are based on communities in defined geographical areas—a small town and a suburb respectively. Prevalence figures for Caerphilly and Speedwell are very similar except in the case of severe chest pain (possible myocardial infarction). Figures for the Regional Heart Study are similar to those for Caerphilly with the possible exception of angina, although this may be explained, in part, by the younger age group in the Regional Heart Study. Prevalence figures for the studies among working

Table 3 *Number (%) of men (and prevalence) by age and past history of possible myocardial infarction*

Area	*Age* 45–49	50–54	55–59	60–63	*Total*
Caerphilly:					
Possible myocardial infarction	72 (8·7)	82 (10·1)	99 (11·3)	—	253 (10·1)
Total number of men	828	811	873	—	2512
Speedwell.					
Possible myocardial infarction	22 (4·9)	51 (7·0)	56 (6·6)	34 (10·7)	163 (6·9)
Total number of men	449	727	854	318	2348

Table 4 *Number (%) of men (and prevalence) by age and electrocardiographic (ECG) evidence of ischaemia*

Area	*Age* 45–49	50–54	55–59	60–63	*Total*
Caerphilly:					
Possible ECG ischaemia	53 (6·4)	89 (11·0)	113 (12·9)	—	255 (10·2)
Probable ECG ischaemia	19 (2·3)	30 (3·7)	49 (5·6)	—	98 (3·9)
All ECG ischaemia	72 (8·7)	119 (14·7)	162 (18·6)	—	353 (14·1)
Total number of men	828	811	873	—	2512
Speedwell					
Possible ECG ischaemia	27 (6·0)	61 (8·4)	115 (13·5)	54 (17·0)	257 (11·0)
Probable ECG ischaemia	9 (2·0)	29 (4·0)	32 (3·7)	18 (5·7)	88 (3·8)
All ECG ischaemia	36 (8·0)	90 (12·4)	147 (17·2)	72 (22·6)	345 (14·7)
Total number of men	449	725*	854	318	2346*

*Two men had no electrocardiogram

populations (Whitehall and the United Kingdom Heart Disease Prevention Project) were uniformly lower than those found in the general population studies. This was particularly so for electrocardiographic ischaemia—both possible and probable.

Discussion

The prevalence of all categories of ischaemic heart disease is very similar in the two areas except for possible myocardial infarction which is much higher in Caerphilly. Because of this the overall prevalence of "any ischaemic heart disease" in Caerphilly is almost 5% higher than in Speedwell. This difference is in the direction that we might expect given the higher mortality from ischaemic heart disease in the Caerphilly area. The standardised mortality ratio for men for ischaemic heart disease in the Rhymney Valley Health District, which contains Caerphilly, averaged 128 over the period 1980 to 1983; for Frenchay Health District (which contains Speedwell) it averaged 95 over the same period. If the higher mortality was reflected by a higher prevalence of ischaemic heart disease then we would have expected all manifestations of the disease to show this higher prevalence. The prevalence of all electrocardiographic evidence of ischaemia is slightly higher in Caerphilly than in Speedwell but, as noted previously, the difference does not achieve statistical significance.

The diagnosis of possible myocardial infarction is based on a positive reply to a single question about prolonged, severe chest pain. Of the 253 men in Caerphilly who answered positively, 108 (43%) either did not see a doctor because of the pain or were told by the doctor that the origin of the pain was non-ischaemic. The corresponding figure in Speedwell was 47 (29%) of 163 men answering positively. This is supported by the fact that in Caerphilly 46% of the 253 men who had had a prolonged, severe, chest pain answered "No" when asked whether they had had a heart attack or coronary thrombosis. The corresponding figure in Speedwell was 42%.

Thus the diagnosis of possible myocardial infarction undoubtedly includes false positives. There is a suggestion from the data above that this false positive rate may be higher in Caerphilly than in Speedwell. In Caerphilly 23% of men with a past history of myocardial infarction also have angina. The corresponding figure in Speedwell is 47%. In Caerphilly, 33% of men with a past history of myo-

Table 5 *Number (%) of men (and prevalence) by age and presence of any ischaemic heart disease (IHD)*

Area	*Age* 45–49	50–54	55–59	60–63	*Total*
Caerphilly.					
Any IHD	159 (19·2)	211 (26·0)	261 (29·9)	—	631 (25·1)
Total number of men	828	811	873	—	2512
Speedwell					
Any IHD	68 (15·1)	158 (21·8)	208 (24·4)	106 (33·3)	540 (23·0)
Total number of men	449	725	853	318	2345*

*Angina category unknown for one man and no electrocardiogram for two men.

Table 6 *Number (%) of men (and prevalence) with individual categories of ischaemic heart disease (45–59 years only)*

Category	*Caerphilly*	*Speedwell**
Angina only	108 (4·3)	75 (3·7)
Possible myocardial infarct only	141 (5·6)	53 (2·6)
ECG ischaemia only	244 (9·7)	201 (9·9)
Angina and possible myocardial infarction	29 (1·2)	33 (1·6)
Angina and ECG ischaemia	26 (1·0)	29 (1·4)
Possible myocardial infarction and ECG ischaemia	54 (2·1)	20 (1·0)
Angina, possible myocardial infarction and ECG ischaemia	29 (1·2)	23 (1·1)
Any ischaemic heart disease	631 (25·1)	434 (21·4)
Total number of men	2512	2027†

*All men aged 60—63 years excluded.
†Angina category unknown for one man and no electrocardiogram for two men.
ECG, electrocardiographic evidence

cardial infarction had electrocardiographic evidence of ischaemia and 17% have probable electrocardiographic evidence of ischaemia. The corresponding figures in Speedwell are again higher at 39% and 20% respectively. These differences are consistent with the hypothesis of a higher false positive rate for possible myocardial infarction in Caerphilly.

Thus there seem to be very minor differences in the prevalence of ischaemic heart disease between Caerphilly and Speedwell despite a substantial difference in mortality. If it is assumed that the community samples are representative of the health districts for which mortality data are available then clearly a higher incidence of ischaemic heart disease would be expected in the Caerphilly sample given the mortality statistics for the Rhymney Valley. Since the prevalence data are very similar in Caerphilly and Speedwell this implies that the case-fatality rates differ in the two communities. Studies of total incidence in communities show that over 50% of deaths from ischaemic heart disease occur outside hospital before medical assistance has been summoned.[7] [8] Clearly many factors operating in or out of hospital may be responsible for different case-fatality rates in the two communities. One possibility is that the effectiveness of community services and hospital treatment may differ between the areas. Another possibility is that some factors present to a greater extent in one area than in the other are more closely associated with fatal cases rather than with surviving cases. In the Regional Heart Study the percentage of heavy smokers in the 24 towns sampled was positively and significantly associated with the standardised mortality ratio for ischaemic heart disease in these towns.[9] It is possible that smoking habit in particular is more closely associated with mortality from ischaemic heart disease than with morbidity: Caerphilly had about 8% more current smokers than Speedwell, and Speedwell had 9% more ex-smokers than Caerphilly.

A comparison of the prevalence of ischaemic heart disease in Caerphilly and Speedwell is facilitated by the common basic protocol of the studies, but comparisons with other British studies (table 7) are hampered by population and methodological differences. Two of the other major studies (Whitehall and United Kingdom Heart Prevention Project) are based on working populations, whereas Caerphilly and Speedwell are based on whole communities which will include both unemployed men and those who have retired early because of ill health. In Caerphilly the men were asked whether they were currently employed or not, and in every age group the prevalence of every category of ischaemic heart disease was higher among men who were not employed. In the youngest men, aged 45–49 years, the prevalence of "any ischaemic heart disease" was 37%, over twice as high as that in employed men. In the two older age groups the prevalence of ischaemic heart disease is about 50% higher among men not currently employed. If the study had been confined to working men aged 45 to 59 years the overall prevalence of ischaemic heart disease would have been about 21·7% compared with the 25·1% actually found in the total population. This factor explains

Table 7 *Prevalence (%) of ischaemic heart disease in middle aged British men*

Age range (yr)	*Caerphilly (45–59)*	*Speedwell (45–59)*	*Regional Heart Study (40–59)*	*Whitehall Study (40–59)*	*UK Heart Disease Prevention Project (40–59)*
Angina	7·6	7·9	4·8	4·3	3·6
Possible myocardial infarction	10·1	6·4	9·1	6·5	6·6
Possible ECG ischaemia	10·2	10·0	11·4	5·0	6·9
Probable ECG ischaemia	3·9*	3·5*	3·1	0·5*	0·9†
Any IHD	25·1	21·4	23·1	14·2	—

*Minnesota codes 1.1 to 1·2.
†Minnesota codes 1·1 to 1·3.

about half the difference in prevalence figures between the community and working populations shown in table 7. There are also methodological differences between these studies. Although the questionnaire definitions of ischaemic heart disease were all based on those used in the Whitehall Study the prevalence figures for electrocardiographic evidence of ischaemia are not comparable. In the Whitehall Study and the United Kingdom Heart Prevention Project six lead electrocardiograms were used and this would result in a minimum of a 25% loss of information for overall myocardial ischaemia and perhaps 50% of Q wave items.[10] Although there were clinical comparative studies of the three lead orthogonal lead and 12 lead electrocardiogram system in the Regional Heart Study[11] a different level of sensitivity may apply. Given the different electrocardiographic methods the prevalence of ischaemia in the Regional Heart Study and the present community studies is very similar.

Taken together, these studies, which span a period of 15 years, clearly indicate a persistently high level of both recognised and unrecognised ischaemic heart disease among middle aged British men. Mortality figures[12] also remain persistently high and further research into this important disease remains a public health priority.

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The effect of treatment of congestive heart failure on plasma atrial natriuretic peptide concentration: a longitudinal study

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SUMMARY Eleven patients with acute congestive heart failure were studied during treatment with a loop diuretic. Plasma concentrations of atrial natriuretic peptide were considerably increased before treatment and with successful treatment returned progressively towards normal values. There was a statistically significant correlation between plasma atrial natriuretic peptide concentration and both jugular venous pressure and change of body weight.

These results support the hypothesis that atrial distension is an important stimulus to atrial natriuretic peptide release. Furthermore, the close relation between plasma concentrations of atrial natriuretic peptide and clinical improvement in these patients suggests that measurement of plasma atrial natriuretic peptide concentration could provide a clinically useful and non-invasive method of monitoring the response to treatment.

Soon after the discovery that high concentrations of peptides with potent natriuretic properties are stored in atrial muscle cells,[1] it was proposed that atrial distension caused by changes of extracellular fluid volume might act as a stimulus to the release of atrial natriuretic peptide into the circulation, and that atrial natriuretic peptide could thus act as a natriuretic hormone.[2] The intravenous infusion of sufficient quantities of saline or colloid to raise atrial pressure has been shown to produce a dose dependent plasma release of atrial natriuretic peptide in laboratory animals[3 4] and human beings.[5] Several cross sectional studies have shown a relation between atrial pressure and plasma atrial natriuretic peptide concentration during cardiac catheterisation procedures.[6–8]

We report the results of a longitudinal study to assess the changes in the plasma concentration of atrial natriuretic peptide before and during the treatment of patients with acute exacerbations of congestive heart failure.

Patients and methods

PATIENTS

Eleven consecutive patients (aged 39–84, mean 69) with acute exacerbations of congestive heart failure were studied. Table 1 shows their diagnoses, drug treatment, and further clinical details. Inclusion criteria for the study were (*a*) a history of increasing breathlessness and orthopnoea; (*b*) clinical signs of an elevated jugular venous pressure and peripheral and pulmonary oedema; (*c*) radiological evidence of left heart failure. Patients who required mechanical ventilation, were too ill to be managed on a general medical ward, or who had evidence of valvar heart disease were excluded. All patients gave their consent to the study which was approved by the hospital ethics committee

Any previous diuretic treatment was stopped on admission but all other medications were continued unchanged. The patients were treated with doses of frusemide (and oral potassium supplements) adjusted to the clinical response. In all cases the jugular venous pressure and body weight were measured and blood samples were taken on admission and thereafter at a similar time of day (either between 10.30 and 11.30 am or between 3.30 and 5.30 pm) on at least four further occasions. Venous pressure

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Table 1 *Clinical details of the patients studied*

Patient	*Sex*	*Age*	*Medications on admission to hospital (daily dose)*	*Aetiology of current episode of heart failure*	*Duration of present symptoms*	*Previous illnesses (year of onset)*	*Symbol used in fig 1*
1	M	68	Salbutamol inhaler, methyldopa (1·5 g), aminophylline (450 mg), frusemide (120 mg), slow release K$^+$	IHD; poor compliance	7 days	Hypertension (1963), chronic bronchitis (1975), myocardial infarct (1978), retinal detachment (1978), recurrent admissions CHF (1978)	▲
2	M	39	Thiamine (100 mg), digoxin (0·25 mg), prazosin (6 mg)	Alcoholic cardiomyopathy	2 weeks	Nil	●
3	F	84	Digoxin (0·0625 mg), isosorbide dinitrate (80 mg), frusemide (40 mg)	Myocardial infarct	3 weeks	Myocardial infarct (1977), atrial fibrillation (1981)	★
4	F	74	Allopurinol (300 mg), warfarin (4 mg), frusemide (80 mg), slow release K$^+$	IHD	3 days	Anterior myocardial infarct (1972), transient ischaemic attack (1976), gout (1981)	○
5	M	78	Aldactide® (2 tab)	Alcoholic cardiomyopathy	4 days	CHF (1985)	▼
6	F	78	Allopurinol (300 mg), moduretic® (2 tab), digoxin (0·125 mg)	IHD, atrial fibrillation	3 weeks	Hypertension (1964), breast cancer (1967), atrial fibrillation (1971), gout (1984)	▽
7	M	64	Isosorbide dinitrate (40 mg), nifedipine (40 mg), frusemide (120 mg)	Myocardial infarct	1 day	Hypertension (1962), myocardial infarct (1977), stroke (1977), recurrent CHF (1982), angina (1984)	△
8	F	64	Aminophylline (450 mg), frusemide (80 mg)	Cor pulmonale	3 days	Chronic bronchitis (1965)	◇
9	M	74	Isosorbide mononitrate (20 mg), salbutamol (4 mg), digoxin (0·125 mg), frusemide (40 mg), spironolactone (100 mg)	IHD, atrial flutter	2 weeks	Chronic bronchitis (1971), hypertension (1982), intermittent claudication (1982), angina (1984), CABG (1984)	◆
10	M	76	Digoxin (0·0625 mg), frusemide (80 mg), amiloride (5 mg)	IHD, atrial fibrillation	3 weeks	CHF (1985), atrial fibrillation (1985)	■
11	M	70	Thyroxine (50 μg), frusemide (40 mg)	Hypothyroidism, IHD	2 weeks	Myocardial infarct (1984)	□

IHD, ischaemic heart disease; CHF, congestive heart failure; CABG, coronary artery bypass graft.

measurements and blood sampling were performed with patients in bed supported at 45° on pillows. Venous pressure was measured visually at the bedside on a vertical centimetre scale to judge the height of the jugular venous pulsation above the angle of Louis.

Observations were continued until the physician in charge of each patient judged on clinical grounds that the patient was fit enough to be discharged from hospital and to continue treatment at home.

BLOOD SAMPLING PROCEDURE AND RADIOIMMUNOASSAY OF ATRIAL NATRIURETIC PEPTIDE

Blood samples (12 ml) were taken into glass tubes containing 60 mg of potassium EDTA and 4000 kallikrein inactivator units of aprotinin (Trasylol, Bayer Pharmaceuticals). The tubes were stored on ice and then centrifuged within 15 minutes of venesection. The plasma was separated and frozen at −20°C until assay. After thawing, atrial natriuretic peptide was extracted from 3 ml volumes of plasma on Sep-pak C18 cartridges (Waters Associates) by a procedure with a mean (SEM) extraction recovery of 79 (2)%.[9] The extracts were evaporated to dryness in a Savant vacuum centrifuge and the pellet was dissolved in 1·2 ml of radioimmunoassay buffer[10] overnight. Volumes (400 μl, 100 μl, and 25 μl) of the reconstituted extracts were assayed in duplicate by a specific radioimmunoassay (using antibody Y2)[10] developed at the Royal Postgraduate Medical School that was capable of detecting 1 pmol/l changes of atrial natriuretic peptide concentration from zero with 95% confidence.[9 10] The plasma atrial natriuetic peptide concentration was not corrected for extraction recovery.

Data are given both as actual values for each individual patient during the course of treatment and as mean (SEM) for all patients at specific time points during treatment. Statistical analysis was by Student's *t* test. Correlation coefficients were calculated by the linear regression technique.

Results

In all patients the jugular venous pressure was considerably elevated and plasma atrial natriuretic peptide concentration was raised on admission and returned progressively towards normal with diuretic treatment (figs 1, 2, and 3). There was a highly significant difference between the initial (80·7 (16·0) pmol/l) and final (18·5 (3·2) pmol/l)) mean values of the plasma atrial natriuretic peptide concentration ($p < 0.001$), jugular venous pressure (initial 8·3 (0·8) and final 2·3 (0·4) cm H_2O, $p < 0.001$) and change of body weight (7·1 (1 8) kg, $p < 0.001$). The time course of the return of the mean plasma atrial natriuretic peptide concentration towards normal values closely paralleled that of both the mean jugular venous pressure and the mean change of body weight (fig 1). Plasma atrial natriuretic peptide concentration showed a close correlation with jugular venous pressure both within individuals (table 2) and within

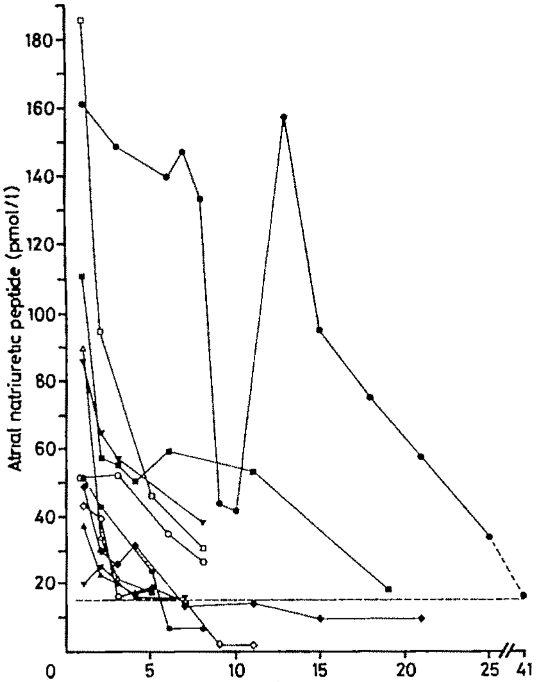

Fig 1 *Mean (SEM) values of plasma atrial natriuretic peptide concentration during diuretic treatment of congestive heart failure for one week in 11 patients. The broken line indicates the upper limit (15 pmol/l) of the normal 9 am fasting plasma atrial natriuretic peptide concentration in recumbent healthy young adults (n = 24)*[10]

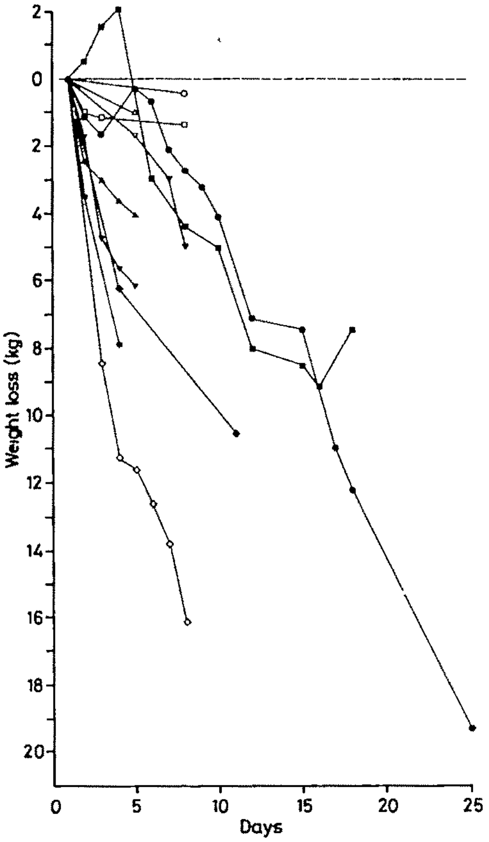

Fig 2 *Mean (SEM) values of loss of body weight during diuretic treatment of congestive heart failure for one week in 11 patients.*

Table 2 *Relation between serial measurements of plasma atrial natriuretic peptide and jugular venous pressure in individual patients*

Patient	*Slope*	*Intercept*	*Correlation coefficient (r)*	*Probability of nul hypothesis (p)*
1	5·0	7·2	0·99	0·001
2	9·8	− 1·2	0·74	0·01
3	6·0	9·4	0·95	0·05
4	9·3	− 9·4	0·95	0·05
5	8·0	16·5	0·60	0·12
6	7·4	21·5	0·97	0·05
7	17·5	22·7	0·96	0·01
8	3·7	− 0·6	0·95	0·001
9	6·2	− 1·5	0·86	0·01
10	14·7	− 5·0	0·89	0·05
11	20·0	19·4	0·99	0·01

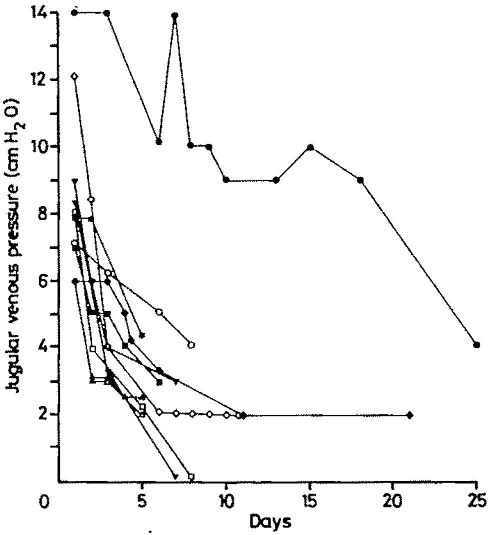

Fig 3 *Mean (SEM) values of jugular venous pressure during diuretic treatment of congestive heart failure for one week in 11 patients.*

the group as a whole (r = 0·62, p < 0·001). Similarly within the group plasma atrial natriuretic peptide concentration correlated significantly with body weight (r = 0·59, p < 0·01). A similar pattern of response to treatment was seen irrespective of the aetiology of the congestive heart failure.

Discussion

Soon after the isolation, sequencing, and synthesis of the atrial peptides, Sagnella and MacGregor postulated that atrial natriuretic peptide was a natriuretic hormone and that atrial distension was a major stimulus to atrial natriuretic peptide release.[2] Evidence supporting this hypothesis includes that of Lang and his colleagues who showed that raising the filling pressure of an isolated heart preparation increased atrial natriuretic peptide release from the heart.[4] Expansion of blood volume with colloidal solution has been shown to release atrial natriuretic peptide into plasma in vivo.[3] More recently in human beings, saline infusion was shown to cause the release of atrial natriuretic peptide into plasma.[5 11] Furthermore, the increase of plasma atrial natriuretic peptide concentration in response to saline infusion correlates closely with changes of right atrial pressure.[5] These studies support Sagnella and MacGregor's hypothesis.

Acute heart failure increases atrial filling pressures and might thus be expected to release increased quantities of atrial natriuretic peptide into plasma. Previous brief reports have described raised plasma atrial natriuretic peptide concentrations in patients with congestive heart failure,[12-14] and the results of cross sectional studies have supported the presence of a link between atrial pressure and atrial natriuretic peptide release.[6-8] The present study goes further and demonstrates a close relation between clinical indices of the severity of heart failure (serial measurement of the jugular venous pressure and of body weight) and circulating concentrations of atrial natriuretic peptide when individual patients are studied longitudinally.

We studied patients presenting consecutively for emergency treatment in hospital and we used specific but broad selection criteria so that our findings would be relevant to routine clinical practice. In this group of patients there was naturally some variation in drug treatment and in the aetiology of the heart failure. The fact that this variability did not prevent a clear relation between the observed indices of the clinical severity of the heart failure and the circulating concentrations of atrial natriuretic peptide from emerging reinforces the general applicability of our observation.

We have shown that plasma concentrations of atrial natriuretic peptide are raised for some days as a result of acute congestive heart failure. The pathophysiological importance of this finding remains to be explained. Clearly the high concentrations of atrial natriuretic peptide were not causing a diuresis and natriuresis of sufficient magnitude to alleviate the condition spontaneously. This may be due in part to the activation of the sodium-conserving renin-angiotensin-aldosterone system that is known to occur in heart failure.[15 16]

Acute congestive heart failure produces sustained increases of atrial pressure. Monitoring of atrial pressure can provide an important guide to clinical management.[17] Thus we speculate that if circulating concentrations of atrial natriuretic peptide are indeed related to atrial distension, as the present study would suggest, monitoring of the plasma atrial natriuretic peptide concentration could provide a clinically useful non-invasive index of the response to treatment. Despite the intense medical and scientific interest generated by the discovery of atrial natriuretic peptide,[18 19] little information of direct relevance to the general physician has so far emerged. We therefore feel that this speculative hypothesis warrants further clinical investigation.

Currently clinical application of plasma atrial natriuretic peptide assays would be limited by the need for plasma extraction and relatively long assay incubation times. The assay used in this study had a two day extraction step followed by a four day incubation. Overnight assay incubation gives acceptable, reproducible, and adequately sensitive (2 fmol/

assay tube) results for patient monitoring. Clearly a goal for the near future is a further reduction in assay times. Radioreceptor assays are already being developed with incubation times of a few hours only[20] and further advances in atrial natriuretic peptide assay technology can be expected.

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Extrapolated maximal oxygen consumption: a new method for the objective analysis of respiratory gas exchange during exercise

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SUMMARY Respiratory gas exchange was measured during maximal treadmill exercise testing in six healthy volunteers and 20 patients with chronic heart failure. A curve of equation $y = ax - bx^2$ was used to model the relation between the rate of oxygen consumption (y axis) and the rate of carbon dioxide production (x axis). The constants "a" and "b" were used to calculate the maximal value of the expression $ax - bx^2$. This value was termed the "extrapolated maximal oxygen consumption". For all subjects a close fit between experimental data and mathematical model was obtained and the values of the measured maximal rate of oxygen consumption and "extrapolated maximal oxygen consumption" were similar. Respiratory gas exchange was reanalysed using only those values obtained during the first 90%, 75%, and 66% of exercise. In contrast with the value for the measured rate of oxygen consumption, the value of "extrapolated maximal oxygen consumption" was effectively independent of exercise duration.

Extrapolated maximal oxygen consumption provides an objective measure of cardiorespiratory functional reserve that, within limits, is independent of exercise duration. Extrapolated maximal oxygen consumption is complementary to the direct measurement of the maximal rate of oxygen consumption and increases the amount of information derived from a single exercise test.

An important problem in the assessment of patients with chronic heart failure is the lack of an objective and effort independent measure of cardiorespiratory functional reserve.[1] In recent years there has been renewed interest in the measurement of the maximum rate of oxygen consumption ($\dot{V}O_2$ max) and anaerobic threshold,[2-4] but both of these measurements have limitations.

Early studies of respiratory gas exchange in patients with chronic heart failure reported that the rate of oxygen consumption ($\dot{V}O_2$) during treadmill exercise reached a plateau before the patient reached maximal workload.[5] This plateau was believed to represent the combination of maximum cardiac output and maximum oxygen extraction by the tissues. Accordingly measurement of $\dot{V}O_2$ max was claimed to provide an objective measure of cardiovascular function. In our experience,[4] and in that of many other laboratories,[1] it is rare to see a true plateau in oxygen consumption during treadmill exercise. Measured $\dot{V}O_2$ max is therefore effort dependent and may be altered by changes in patient motivation or supervisor encouragement. In consequence, $\dot{V}O_2$ max is essentially a symptom limited measurement of exercise tolerance and, as such, will reflect not only cardiorespiratory functional reserve but also the individual's perception and tolerance of symptoms.

The supply of energy to working skeletal muscle by anaerobic metabolism increases with workload. The mechanisms responsible for this transition are complex,[6] but are at least in part caused by inadequate blood supply to active muscle.[6-8] Anaerobic metabolism produces lactic acid which is buffered by bicarbonate with the consequent liberation of carbon dioxide. Thus the rate of carbon dioxide production ($\dot{V}CO_2$) rises disproportionately to $\dot{V}O_2$. The definition of the anaerobic threshold is an attempt to attribute the onset of anaerobic metabolism to a specific point during exercise.[7] Most commonly anaerobic threshold is determined subjectively as the

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supposed point during exercise at which the relation between $\dot{V}CO_2$ and $\dot{V}O_2$ departs from linearity.[9 10] This form of analysis is unsatisfactory on two counts—first because it is subjective and secondly because there is a range of anaerobic metabolism that alters in rate rather than starting and stopping at a fixed workload.

In an attempt to obtain an objective measurement of cardiorespiratory functional reserve that is independent of exercise duration we have developed a new method for the analysis of respiratory gas exchange during exercise. Our method resembles that used to determine anaerobic threshold in that it uses the non-linear relation between $\dot{V}O_2$ and $\dot{V}CO_2$ that occurs with increasing workload. In contrast with anaerobic threshold our method does not attempt to attribute the onset of anaerobic metabolism to a fixed point during exercise. Instead the relation between $\dot{V}O_2$ and $\dot{V}CO_2$ is analysed by means of curve fitting. The curve is then extrapolated mathematically to determine the theoretical maximal value that oxygen consumption can attain. We have named this measurement the "extrapolated maximum oxygen consumption". We describe the method and compare its results with those of the conventional measurement of $\dot{V}O_2$ max.

Patients and methods

We studied six healthy volunteers and 20 patients with chronic stable heart failure. Table 1 shows age, sex, diagnosis, and $\dot{V}O_2$ max of each subject. All subjects were selected because of their ability to perform maximal symptom limited, treadmill exercise testing that fulfilled the following criteria. Exercise was limited by fatigue or shortness of breath or both. Patients exercised for at least four minutes. The respiratory exchange ratio rose progressively during exercise, reaching a value > 1 for at least the last 30 seconds of exercise. The last criterion was used to ensure that a level of exercise had been achieved that stressed cardiovascular function.[11]

Patients with myocardial infarction during the preceding three months, evidence of myocardial ischaemia or ventricular arrythmias during exercise, obstructive valvar heart disease, hypertrophic cardiomyopathy, or appreciable pulmonary disease (documented by lung function tests) were excluded from the study.

EXERCISE TEST

Exercise tests were performed by the modified Bruce protocol, in an air conditioned laboratory, with room

Table 1 *Individual results for the full duration of exercise for $\dot{V}O_2$ max (measured maximal rate of oxygen consumption), r (correlation coefficient for curve fitting), and extrapolated maximal oxygen consumption (EMOC)*

Subject	*Age*	*Sex*	*Diagnosis*	*$\dot{V}O_2$ max*	*r*	*EMOC*	*$\dot{V}O_2$* max/EMOC%
1	25	M	Normal	49·4	−0·94	52·2	94·7
2	33	F	Normal	39·8	−0·94	44·7	89·0
3	30	M	Normal	37·1	−0·94	36·1	102·8
4	29	F	Normal	33·7	−0·93	34·9	96·9
5	29	M	Normal	33·6	−0·94	36·8	91·4
6	27	F	Normal	26·8	−0·97	27·1	98·0
7	60	M	AVR	24·7	−0·94	24·7	99·9
8	53	M	IHD	23·1	−0·94	22·9	100·8
9	32	M	IHD	22·6	−0·93	24·2	93·0
10	57	M	MR	21·3	−0·89	23·6	90·6
11	29	F	COCM	21·3	−0·98	20·9	102·0
12	45	M	Sarcoid	20·0	−0·95	19·9	100·5
13	50	M	IHD	19·1	−0·96	19·9	96·0
14	57	M	COCM	18·4	−0·97	18·9	97·4
15	57	M	COCM	16·5	−0·92	17·3	95·4
16	65	M	AVR	14·7	−0·86	15·1	97·3
17	41	M	COCM	14·6	−0·85	17·2	85·1
18	50	M	IHD	13·7	−0·86	14·5	94·4
19	29	F	COCM	13·4	−0·89	13·9	96·2
20	51	M	COCM	13·1	−0·79	12·7	102·7
21	54	F	IHD	12·8	−0·79	14·3	90·0
22	44	M	AVR	12·7	−0·96	13·3	95·3
23	59	F	IHD	12·6	−0·93	14·6	86·6
24	53	M	IHD	12·0	−0·73	12·7	94·5
25	56	M	IHD	9·7	−0·88	9·9	98·1
26	49	M	IHD	9·6	−0·90	10·1	95·8
Maximum	65	—	—	49·4	−0·73	52·2	102·8
Minimum	25	—	—	9·6	−0·98	9·9	85·1
Mean	—	—	—	—	−0·91	—	95·6
SD	—	—	—	—	0·06	—	4·7

AVR, after aortic valve replacement; IHD, ischaemic heart disease, MR, mitral reflux; COCM, congestive cardiomyopathy temperature maintained in the range 20–21°C. All subjects had been previously familiarised with treadmill exercise and measurement of respiratory gas exchange. Patients continued their normal medication on the day of exercise tests and all tests were performed at least three hours after meals.

Minute ventilation (VE), $\dot{V}O_2$, and $\dot{V}CO_2$ were measured continuously by the method of Davies and Dennison.[12] Validation and reproducibility of this method in our laboratory has already been described.[4] In brief, subjects were required to breathe through a two way respiratory valve (Collins) held by an adjustable head support. The expiratory port was connected, via flexible tubing, to a 7 litre mixing box (Airspec). Argon was added to the inlet port of the mixing box at a constant flow rate. After full mixing, the resulting gas mixture was continuously analysed by a mass spectrometer (Airspec 200 MGE). The analogue output from the mass spectrometer was fed to the analogue to digital input channels of a microcomputer (BBC model B). Analogue to digital conversions were performed every 200 ms for each of the four channels (nitrogen, oxygen, carbon dioxide, and argon). Every 10 s, a mean value for each channel was calculated, and from these mean values of minute ventilation, $\dot{V}O_2$, $\dot{V}CO_2$, and respiratory exchange ratio were calculated. Values were corrected for atmospheric pressure, laboratory temperature, water vapour pressure, and body weight so as to give the following dimensions: $\dot{V}O_2$ and $\dot{V}CO_2$ in ml/kg/min at standard temperature and pressure (dry); minute ventilation as l/min at body temperature, pressure (prevailing atmospheric), and saturation (water vapour); and the respiratory exchange ratio.

DATA ANALYSIS

$\dot{V}O_2$ max was defined as the maximal mean value of $\dot{V}O_2$ over a 30 second period. The relation between $\dot{V}O_2$ and $\dot{V}CO_2$ was analysed by curve fitting. The mathematical model that was used is given by the equation $y = ax - bx^2$ where x and y represent $\dot{V}CO_2$ and $\dot{V}O_2$ respectively. The equation describes a curve with two components (fig 1). Firstly, a linear component, given by the equation $y = ax$, that passes through the origin and has a slope determined by the constant "a". The value of "a" represents the ratio of $\dot{V}O_2$ to $\dot{V}CO_2$ at the start of exercise (the reciprocal of the resting respiratory quotient). Secondly, a nonlinear component, given by the equation $y = bx^2$, the rate of rise of this expression being determined by the value of the constant "b". By subtracting the second component from the first a progressive deviation from linearity was obtained. The rate of deviation from linearity, determined by the value of "b", was used to model the disproportionate increase in $\dot{V}CO_2$ relative to $\dot{V}O_2$ that occurred with increasing workload.

For each set of $\dot{V}O_2/\dot{V}CO_2$ data the values of "a" and "b" that provided the "best fit" curve were determined. The method (fig 2) used a linear transformation followed by least squares linear regression. The correlation coefficient (r) provided a measure of the accuracy of fit between the mathematical model and the raw data.

Once determined, the values of "a" and "b" were used to calculate the maximal value that the equation $y = ax - bx^2$ could attain. The calculation was in effect an extrapolation of the fitted curve to its maximum value. This value was named the extrapolated maximum oxygen consumption. The mathematical derivation of extrapolated maximal oxygen consumption is shown below:

$$y = ax - bx^2 \qquad (1)$$
$$dy/dx = a - 2bx \qquad (2)$$
$$dy/dx = 0 \text{ when } x = a/2b \qquad (3)$$

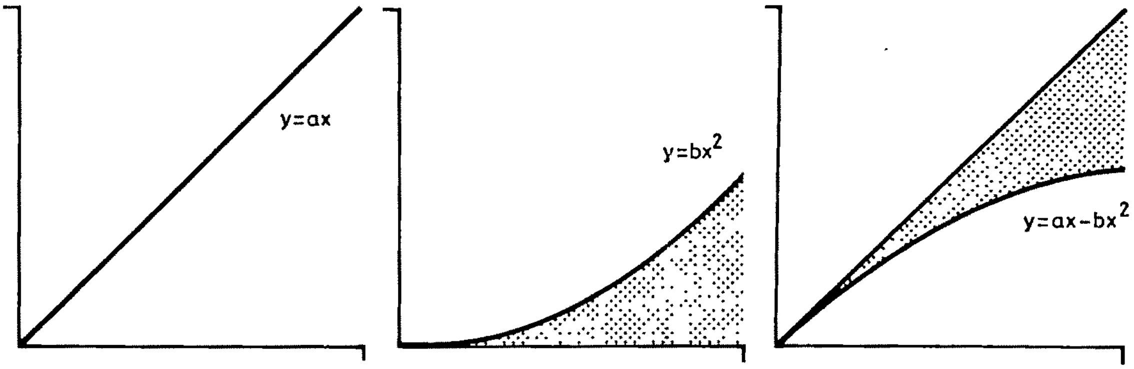

Fig 1 *Illustration of the two components of the equation* $y = ax - bx^2$ *(see text for explanation).*

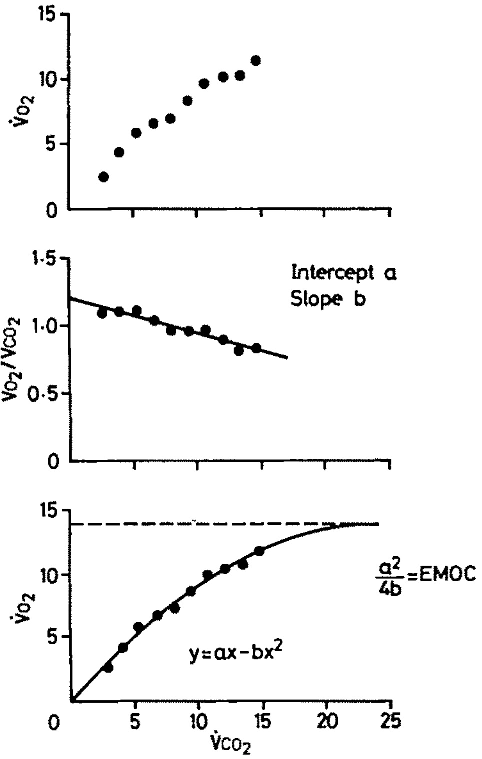

Fig 2 *Method used for curve fitting. The upper graph is a set of raw data for oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) during a single exercise test. The middle graph shows the linear transformation and least squares linear regression analysis used to determine the values of the constants "a" and "b". The lower graph shows the fitted curve and the derivation of extrapolated maximal oxygen consumption (EMOC).*

substituting (3) into (1)
$y = a^2/2b - ba^2/4b^2$
which simplifies to $y = a^2/4b$

therefore extrapolated maximal oxygen consumption = $a^2/4b$.

In order to investigate the relative dependence of extrapolated maximal oxygen consumption and $\dot{V}O_2$ on exercise duration, data from each subject were reanalysed using only those values obtained during the first 90% of exercise duration, the first 75% of exercise duration, and the first 66% of exercise duration. During each reanalysis, the methodology used was identical to that used for analysis of the full exercise duration.

Results

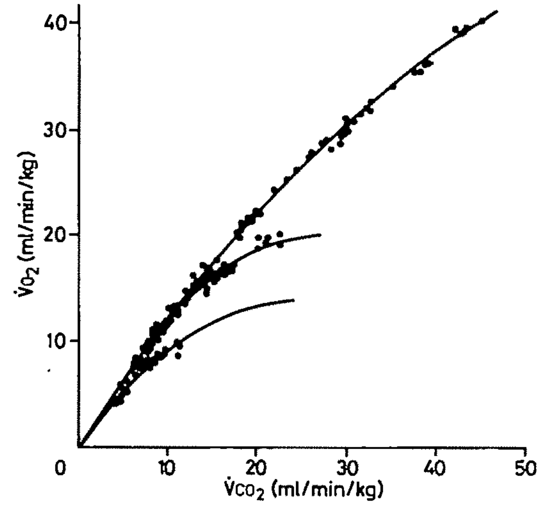

Fig 3 *Relation between the rate of oxygen consumption ($\dot{V}O_2$) and the rate of carbon dioxide production ($\dot{V}CO_2$) for a healthy subject (upper curve), a patient with mild chronic heart failure, and a patient with severe chronic heart failure (middle and lower curves respectively). The "best fit" curve has been superimposed on each set of data.*

All exercise tests were performed without complication. Figure 3 shows examples of $\dot{V}O_2/\dot{V}CO_2$ data with the fitted curves superimposed. Table 1 shows the individual results for the full exercise duration. $\dot{V}O_2$ max ranged from 9·6 to 49·4 ml/min/kg. Extrapolated maximal oxygen consumption ranged from 9·9 ml/min/kg to 52·2 ml/min/kg and correlated closely with $\dot{V}O_2$ max ($r = 0{\cdot}99$, $p < 0{\cdot}001$). The mean value of $\dot{V}O_2$ max expressed as a percentage of extrapolated maximal oxygen consumption was 95 6 (4 7%) with a range of 85·1% to 102·8%. The mean correlation coefficient for curve fitting was 0·91 (0·06) (range 0 73 to 0·98).

REPRODUCIBILITY OF EXTRAPOLATED MAXIMAL OXYGEN CONSUMPTION

Twelve subjects (three controls and nine patients) underwent a second exercise test in order to determine the reproducibility of extrapolated maximal oxygen consumption. When the second exercise test was compared with the first there was no relation between the error variance and extrapolated maximal oxygen consumption ($r = 0{\cdot}06$). Therefore the group was analysed as a whole. The retest reliability coefficient for extrapolated maximal oxygen consumption was 92·8%.

DEPENDENCE OF EXTRAPOLATED MAXIMAL OXYGEN CONSUMPTION AND $\dot{V}O_2$ ON EXERCISE DURATION

Table 2 gives the results for the three subsequent

Table 2 *Individual results for intermediate durations of exercise*

	90% exercise duration				*75% exercise duration*				*66% exercise duration*			
Subject	$\dot{V}O_2$	$\%\dot{V}O_2max$	*EMOC*	*%EMOC 100*	$\dot{V}O_2$	$\%VO_2max$	*EMOC*	*%EMOC 100*	$\dot{V}O_2$	$\%\dot{V}O_2max$	*EMOC*	*%EMOC*
1	44·4	89·8	48·6	93·1	32·6	65·9	41·7	80·0	28·9	58·5	40·8	78·2
2	33·8	84·9	42·0	94·0	29·1	73·2	42·9	96·0	29·1	73·2	47·8	106·9
3	34·1	91·8	35·3	97·8	29·4	79·3	35·4	98·0	23·8	64·1	35·0	96·9
4	30·8	91·3	34·3	98·2	24·6	73·0	36·1	103·5	23·3	69·1		
5	30·7	91·2	35·2	95·7	23·0	68·4	32·1	87·2	21·0	62·5	30·8	83·6
6	26·1	97·6	26·6	98·3	22·5	84·1	25·7	94·9	20·1	75·2	26·0	96·0
7	23·5	94·9	24·4	98·5	22·7	92·0	24·2	97·7	20·7	83·9	23·9	96·5
8	20·5	88·6	22·2	97·2	18·2	78·9	22·6	98·6	16·4	71·1	22·2	97·1
9	21·1	93·7	23·7	97·9	19·7	87·1	22·8	94·0	16·7	74·2	21·2	87·5
10	19·8	92·9	23·2	98·3	16·9	79·3	22·8	96·7	16·9	79·3	25·1	106·4
11	20·2	94·7	20·7	98·9	19·0	89·3	20·5	98·0	17·5	82·0	20·5	98·0
12	18·2	91·0	19·2	96·7	16·7	83·5	19·0	95·5	16·5	82·7	19·0	95·4
13	18·3	95·6	20·9	104·9	16·0	83·8	21·4	107·5	15·1	78·8	22·6	113·6
14	17·3	94·0	18·3	96·9	15·9	86·8	18·2	96·2	15·1	82·4	18·9	100·3
15	16·5	99·8	18·0	104·2	14·8	89·6	20·2	116·5	13·9	84·0		
16	13·9	95·1	15·2	100·8	13·3	90·9	15·7	104·0	12·3	83·9		
17	13·6	93·1	17·0	98·6	12·7	86·7	16·4	95·4	11·4	77·9		
18	13·7	100·0	14·4	98·8	13·2	95·8	14·5	99·7	13·2	95·8		
19	13·2	99·0	14·1	101·7	12·3	91·8	14·8	106·2	11·4	84·8		
20	11·8	90·6	11·6	91·6	11·8	90·6	11·6	91·5	11·8	90·6	11·7	91·7
21	12·2	95·2	14·7	103·3	12·0	93·5			11·9	92·4		
22	11·9	93·5	13·3	100·2	11·6	91·6	15·0	112·8	10·4	82·0	15·5	116·7
23	11·9	93·9	15·1	103·2	11·4	90·6	16·7	114·7	11·4	90·1		
24	12·0	100·0	13·0	102·4	12·0	100·0	14·6	115·1	11·3	94·8		
25	9·4	96·5	9·5	96·1	9·3	95·6	9·4	94·9	9·3	95·6	9·3	93·7
26	8·8	91·7	10·5	104·8	8·8	91·2	10·5	104·3	8·5	88·0	10·1	100·0
Max	44·4	100·0	48·6	104·9	32·6	100·0	42·9	116·5	29·1	95·8	47·8	116·7
Min	8·8	84·9	9·5	91·6	8·8	65·9	9·4	80·0	8·5	58·5	9·3	78·2
Mean		93·9		98·9		85·9		100·0		80·6		97·6
SD		3·6		3·5		8·6		8·7		10·1		9·8

$\dot{V}o_2$, measured rate of oxygen consumption; $\%Vo_2max$, rate of oxygen consumption expressed as a percentage of the measured maximal rate of oxygen consumption; EMOC, extrapolated maximal oxygen consumption; %EMOC 100, extrapolated maximal oxygen consumption expressed as percentage of the value obtained with data for full exercise duration.

analyses of data for intermediate exercise durations. For each reanalysis the resulting values for $\dot{V}o_2$ and extropolated maximal oxygen consumption are given in both absolute units (ml/min/kg standard temperature and pressure (dry)) and as a percentage of the respective values for full exercise duration. Extrapolated maximal oxygen consumption was only calculated if the correlation coefficient (r) for the fitted curve was >0·70. These criteria excluded nine subjects (1 control and eight patients) from the 66% analysis and one patient from the 75% analysis. Figure 4 summarises the results. Over the range of exercise duration studied $\dot{V}o_2$ was linearly related to exercise duration. At 66% exercise duration the mean value of $\dot{V}o_2$ was approximately 80% of the value for $\dot{V}o_2$ max. In contrast, extrapolated maximal oxygen consumption was effectively independent of exercise duration over the same range.

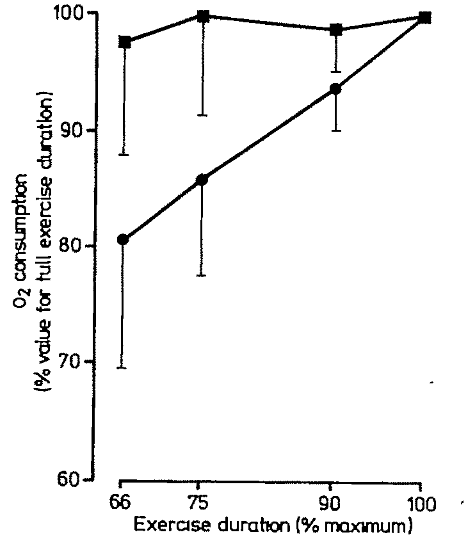

Fig 4 *Graphs showing the degree of dependence of measured oxygen consumption (●) and extrapolated maximal oxygen consumption (■) on exercise duration. Values are the mean for all 26 subjects. Bars represent one standard deviation.*

Discussion

Maximal exercise tests are difficult to perform, even for normal subjects, and unpleasant for subjects and patients alike. The common limiting symptoms are breathlessness and fatigue. The end point of a maximal exercise test (whether measured as duration, workload, or $\dot{V}o_2$ max) is unlikely to represent a standard end point for different individuals. Furthermore, the reproducibility of a symptom limited variable (desirable as it is for the assessment of response to treatment) adds no information about the cause or mechanism of limitation. For example, a stoic may repeatedly perform "truly" maximal exercise, whereas another individual with identical cardiorespiratory reserve may consistently stop at much lower levels of symptoms. It follows that if an absolute measure of cardiorespiratory functional capacity is required it should not depend purely on measure-ment of limitation caused by symptoms.

In this paper we present a new method for the analysis of respiratory gas exchange during exercise. This method provided an objective measurement of cardiorespiratory functional reserve that, within limits, was independent of exercise duration. We also showed that extrapolated maximal oxygen consumption correlated closely with $\dot{V}o_2$ max ($r = 0{\cdot}99$ $p < 0{\cdot}001$) in a study population selected for their ability to perform exercise that stressed cardiorespiratory function.

On average $\dot{V}o_2$ max was 4·4% lower than extrapolated maximal oxygen consumption and no subject achieved a value of $\dot{V}o_2$ max that was significantly greater than the value of extrapolated maximal oxygen consumption. These two findings add further support to the concept that extrapolated maximal oxygen consumptions provides a measurement of cardiorespiratory reserve.

Inherent in the calculation of extrapolated maximal oxygen consumption is the fact that respiratory exchange at extrapolated maximal oxygen consumption was double that at the onset of exercise (that is a/2). In non-mathematical terms, extrapolated maximal oxygen consumption may be envisaged as the value of $\dot{V}o_2$ obtained by extrapolating the relation between $\dot{V}o_2$ and $\dot{V}co_2$ to the point at which respiratory exchange has risen to double the value at the start of exercise. Clearly it is essential that the curve accurately fits the raw data. The mean correlation coefficient of 0·91 obtained with the equation $y = ax - bx^2$ supports the use of this model. To obtain a value for extrapolated maximal oxygen consumption it is not necessary for the subject to exercise to these values of $\dot{V}o_2$ or respiratory exchange (which may be symptomatically intolerable if not physiologically impossible). It is only necessary to obtain sufficient data accurately to fit the curve.

We do not regard extrapolated maximal oxygen consumption as a replacement for $\dot{V}o_2$ max but rather as a complementary measurement that allows more information to be extracted from a single exercise test. If the values of $\dot{V}o_2$ max and extrapolated maximal oxygen consumption are similar this is evidence that the subject has performed close to "truly" maximal exercise. Alternatively, if the values are widely separated, it is likely that the subject either has a low threshold for symptoms or was limited by factors other than cardiorespiratory function. Because extrapolated maximal oxygen consumption is relatively independent of exercise duration it may avoid spurious variation in measured exercise capacity caused by differences in motivation or supervisor encouragement.

The equation $y = ax - bx^2$ provides an accurate mathematical model for the analysis of respiratory gas exchange during exercise. With this model it is possible to derive a measurement of cardiorespiratory functional reserve that is, within limits, independent of exercise duration. This measurement is complementary to $\dot{V}o_2$ max and greatly enhances the information obtained from a single exercise test.

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Radionuclide measurements of diastolic function for assessing early left ventricular abnormalities in the hypertensive patient

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SUMMARY Three measurements of diastolic filling were compared in 29 patients with essential hypertension and 27 age matched normotensive controls. Systolic function was normal in all but one of the patients. The mean (1SD) first one third filling fraction (a measurement of early diastolic filling) was significantly lower in the hypertensive groups (0·27 (0·24)) than in the control group (0·45 (0·16)). The hypertensive group was subdivided into those with electrocardiographic abnormalities and those without. In the subgroup with a normal electrocardiogram the mean (1SD) first one third filling fraction measurement (0·28 (0·16)) was significantly lower than in the control group. In the subgroup with an abnormal electrocardiogram, the first one third filling fraction was even lower (0·24 (0·9)). In addition, the time to peak filling rate (213 (56) ms) was significantly longer in the subgroup with the abnormal electrocardiogram than in the control group (164 (45) ms). However, the interobserver reproducibility of the time to peak filling measurement was poor. The peak filling rate was low in the subgroup with an abnormal electrocardiogram, but not significantly different from the normal controls. The discriminatory value of the three diastolic measurements did not improve with exercise.

These results showed an early diastolic filling abnormality in essential hypertension that did not appear to be caused by disease of the large coronary vessels as it was present in patients with normal wall motion and a normal exercise electrocardiogram. The occurrence of diastolic abnormalities when systolic function is still normal may mark an early stage in the development of hypertensive heart failure, at a time when the process is still potentially reversible.

The Framingham study[1 2] demonstrated that some degree of arterial hypertension precedes heart failure in 75% of patients who present with this condition. Furthermore, when cardiovascular events occur, they are more likely to be fatal in hypertensive subjects, particularly in those with coexisting left ventricular hypertrophy. Early detection of the effects of high blood pressure upon the heart may therefore be important in preventive treatment. Although left ventricular angiography allows accurate measurement of wall thickness,[3 4] this invasive investigation with its attendant risks is clearly not appropriate for most patients with uncomplicated hypertension. Echocardiography is non-invasive and has been shown to be more sensitive than the electrocardiogram for the detection of structural abnormalities in hypertensive patients.[5] Measurements of wall thickness correlate well with those obtained at operation[6] and during contrast angiography[7] but attempts at measuring left ventricular function by echocardiography have produced contradictory results. For example, one group of investigators found an increased velocity of circumferential fibre shortening in patients with left ventricular hypertrophy,[8] while another group reported normal left ventricular performance in similar patients.[9]

Echocardiographic abnormalities described in mild hypertension include a delayed increase in diastolic dimensions, late mitral valve opening,[10] and a reduction in left ventricular chamber size, despite normal wall thickness.[11] Invasive studies in

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comparable patients have shown normal left ventricular systolic function and normal end diastolic pressure.[12] Considered together these observations suggest that reduced left ventricular compliance precedes the development of systolic abnormalities in the development of hypertensive heart disease. The suggestion that ventricular compliance is abnormal in hypertension is supported by studies in animals relating increased collagen and decreased elastin and glycoprotein to impaired diastolic relaxation.[13]

Recently, abnormal indices of left ventricular filling in hypertension have been reported by workers using the non-imaging nuclear probe[14] and the gamma camera.[15] These techniques offer the prospect of serial, non-invasive measurements of diastolic function which would permit the assessment of the effects of interventions such as drug treatment of hypertension.

We have examined the usefulness of radionuclide measurements of diastolic function by comparing the values obtained in normal subjects with measurements from patients with hypertension, at rest and during exercise.

Patients and methods

Twenty nine hypertensive patients with a diastolic blood pressure of > 95 mm Hg on two occasions after two weeks without treatment were recruited from the Harrow Hypertension Clinic. All had essential hypertension, diagnosed by clinical and laboratory exclusion of secondary causes.

Twenty seven normal volunteers were chosen as an age matched control population. All were symptom free with no history of heart disease and a resting blood pressure of < 140/90 mm Hg. None was taking any cardioactive medication, and all had a normal 12 lead electrocardiogram, a negative symptom limited exercise test (leads CM5 and CC5), and normal left ventricular wall motion during radionuclide angiography.

Equilibrium gated radionuclide angiography was recorded from patients and volunteers with an Elscint Apex 215 M digital gamma camera fitted with an all purpose collimator. The photopeak was set at 140 keV with a 20% window. The blood pool was labelled by an intravenous injection of stannous pyrophosphate, followed 30 minutes later by 740 MBq of technetium-99 m pertechnetate, pre-mixed with the subject's own blood in the syringe. The subjects lay supine on a bicycle exercise system while resting 24 frame anterior views and 32 frame left anterior oblique views were recorded. For the acquisition of left anterior oblique views the camera was positioned with a 10°–15° caudal tilt (as required) to obtain optimum separation of the ventricles and to remove overlap caused by the left atrial blood pool. Five million counts were recorded using electrocardiographic gating with a 5% RR interval tolerance to exclude the effects of extrasystoles and sinus arrhythmia. After data collection at rest the subjects underwent graded, symptom limited, bicycle exercise. The initial workload of 25 W was increased by 25 W every three minutes, and a 24 frame left anterior oblique acquisition of at least three million counts was recorded during the last stage of exercise using electrocardiographic gating with a 15% RR interval tolerance. The tests were terminated when the patients complained of fatigue, dyspnoea, or angina, or when the normal subjects developed fatigue or dyspnoea. The electrocardiogram was monitored continuously. Leads CM5 and CC5 were recorded at the end of every three minutes during exercise, at peak exercise, and at the end of each minute during 5 minutes of recovery.

The radionuclide data were analysed by two independent observers. After time correction and smoothing, a continuous loop cineangiogram was constructed and examined for wall motion abnormalities. Individual left ventricular regions of interest were identified in each frame of the left anterior oblique studies by a semiautomatic, second derivative, edge-seeking algorithm which has been shown to produce excellent inter- and intraobserver repeatability.[16] An adjacent background region was identified in the end systolic frame and subtracted from the data before a high resolution time-activity curve was plotted. The 32 frames and narrow electrocardiographic gating tolerance ensured good preservation of the diastolic portion of the curve. This time-activity curve was differentiated to assist with identification of the maximum filling point early in diastole, and the following measurements were calculated as described elsewhere[15 17]: (*a*) ejection fraction (end diastolic counts – end systolic counts/end diastolic counts); (*b*) peak filling rate normalised to end diastolic counts (end diastolic counts/s); (*c*) time to peak filling (ms); (*d*) first one third filling fraction (stroke counts in first third of diastole/total stroke counts × RR interval).

An earlier study in our laboratory showed excellent reproducibility of diastolic function measurements by the semiautomatic radionuclide method developed in the Elscint computer.[17] Seventeen patients with chronic stable angina underwent two radionuclide studies each at the end of two week placebo treatment. The two placebo periods were before and after a four week treatment period with an antianginal agent (carvedilol). Indices of diastolic left ventricular function for the two placebo periods were: peak filling rate 1·9 (0·2) and 1·9 (0·2) end diastolic volumes per second; early filling rate 0·9

Table 1 *Mean (SD) interobserver difference of radionuclide measurement of left ventricular systolic and diastolic function at rest and during exercise in 23 hypertensive patients*

Measurement	*Rest*	*Exercise*
Ejection fraction	−0·26 (3·23)	+1·05 (6·38)
Peak filling rate	−0·09 (0·34)	+0·16 (0·61)
Time to peak filling rate	+0·02* (0·03)	0·00 (0·02)
One third filling fraction	−0·01 (0·06)	0·00 (0·14)

*$p < 0{\cdot}05$.

(0·1) and 0·9 (0·1) end diastolic volumes per second; first third filling fraction 0·29 (0·03) and 0·37 (0·05) (p = NS).[17]

The blood pressure of the hypertensive subjects was recorded with a Hawksley random zero sphygmomanometer after they had rested quietly for 15 minutes; the systolic blood pressure was also recorded during the exercise tests using an anaeroid sphygmomanometer.

The electrocardiograms were analysed by an observer who was unaware of the other results. The criteria of Romhilt and Estes were used to diagnose left ventricular hypertrophy.[18] Ischaemia was diagnosed from the exercise test if the subjects developed planar or downsloping ST segment depression of 1·5 mm or more below the resting level 60 ms after the J point.

Results within groups were compared by Student's paired *t* test, and between groups by Student's unpaired *t* test (both two tailed). Individual variables were compared by linear correlation analysis.

Results

There were 27 healthy volunteers (11 men and 16 women) with a mean age of 49 years (range 40–74 years). There were 29 hypertensive patients (24 men and 5 women, mean age of 53 years (range 39–70 years)). The age difference was not statistically significant.

Table 1 shows the mean interobserver differences in the diastolic function measurements from 23 hypertensive patients, together with the statistical significance of these differences. The time to peak filling rate showed a mean (SD) interobserver difference of 20 (30) ms ($p<0{\cdot}05$).

The resting ejection fraction measurements of the control and the hypertensive groups were compared. The mean (SD) resting ejection fraction of the hypertensives of 59·9 (9·4)% was not significantly different from the value of 58·7 (8·4)% in the controls (tables 2 and 3). The ejection fraction was below the normal range in one hypertensive patient, who had a normal rest and exercise electrocardiogram and normal wall motion (table 4).

In fig 1 the peak filling rate of the two groups is compared. The mean (SD) value for the controls (2·57 (0·42) end diastolic volumes per second) was not statistically different from that of the hypertensive patients (2·56 (0·78)) (tables 2 and 3).

Figure 2 compares the time to peak filling rate in the two groups. The mean (SD) times to peak filling in the controls (164 (45) ms) and hypertensive patients (186 (51) ms) were not significantly different (tables 2 and 3).

Figure 3 shows the first one third filling fraction in the two groups. The mean (SD) first one third filling fraction in the hypertensive group (0·27 (0·14)) was significantly lower than in the control group (0·45 (0·26)) ($p<0{\cdot}001$, table 3).

The group with hypertension was subdivided into

Table 2 *Radionuclide measurements (mean (SD)) of left ventricular systolic and diastolic function at rest and during exercise in 27 controls and 29 hypertensive patients and subgroups of 12 hypertensive patients with abnormal electrocardiograms and 17 hypertensive patients with normal electrocardiograms*

	Controls		*Patients with hypertension*					
			All		*Abnormal ECG*		*Normal ECG*	
	Rest	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*
No	27	24	29	27	12	10	17	16
Age (years)	48·8 (7·6)		53·1 (9·3)		54·1 (10·9)		52·1 (8·3)	
Ejection fraction (%)	58·7 (8·4)	62·5 (9·1)	59·5 (9·4)	61·4 (8·3)	61·6 (11·2)	60·1 (8·9)	58 (7·8)	62·3 (8)
Peak filling rate (EDV/s)	2·57 (0·42)	5·77 (1·39)	2·56 (0·78)	5·28 (1·41)	2·45 (0·78)	5·87 (1·74)	2·64 (0·79)	4·92 (1·07)
Time to peak filling (ms)	164 (45)	116 (30)	186 (51)	109 (34)	213 (56)	101 (34)	168 (38)	114 (34)
First one third filling fraction	0·447 (0·160)	0·404 (0·167)	0·266 (0·139)	0·479 (0·225)	0·243 (0·092)	0·518 (0·232)	0·282 (0·164)	0·445 (0·244)
Heart rate (beats/min)	69·1 (9·9)	139·3 (22·3)	78·3 (14·8)	130·9 (19·7)	75·4 (13·3)	134·1 (22·5)	79·7 (16·0)	128·6 (17·9)

ECG, electrocardiogram; EDV, end diastolic volume

Table 3 *Statistical significance of comparisons of groups in table 2 by unpaired* t *tests*

	Controls vs total hypersensitive groups		*Controls vs hypersensitive patients with abnormal ECG*		*Controls vs hypersensitive patients with normal ECG*		*Hypersensitive patients with normal ECG vs those with abnormal ECG*	
	Rest	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*
Ejection fraction	NS	NS	NS	NS	NS	NS	NS	NS
Peak filling rate	NS	NS	NS	NS	NS	<0·05	NS	NS
Time to peak filling rate	NS	NS	<0·01	NS	NS	NS	<0·02	NS
One third filling fraction	<0·001	NS	<0·001	NS	<0·002	NS	NS	NS
Heart rate	<0·01	NS	NS	NS	<0·01	NS	NS	NS

None of the age differences between any of the groups was significant.

those patients with a normal electrocardiogram and those showing a definite abnormality of either the rest or the exercise electrocardiogram. Table 4 lists these individual electrocardiographic abnormalities together with the abnormalities of radionuclide measurements (defined as any value outside the normal range). Twelve patients had abnormalities of the electrocardiogram: three (25%) had resting ST segment depression, eight (67%) developed ST depression of ≥1·0 mm during exercise, and six (50%) had evidence of left ventricular hypertrophy (see open circles in figs 1–3).

Wall motion abnormalities were evident during radionuclide angiography in five patients; four of these also had an abnormal electrocardiogram (table 4).

Ten patients with hypertension had first one third filling fractions that were below the lower limit measured in the controls; six of these ten patients had a normal electrocardiogram. This measurement was low in the patient with a depressed ejection fraction. The peak filling rate was depressed in five patients: two with a normal electrocardiogram and three with an abnormal electrocardiogram. Two of these three also had abnormal wall motion and ST segment depression on exercise. The time to peak filling rate was prolonged in only one patient, who also had an abnormal rest and exercise electrocardiogram, abnormal wall motion, and depression of the peak filling rate. There was no overlap between the subjects with depression of the peak filling rate and those with a low first one third filling fraction.

Of the six patients with voltage criteria of left ventricular hypertrophy, two had an abnormal peak

Table 4 *Electrocardiographic abnormalities, wall motion, systolic and diastolic function abnormalities in 20 patients with hypertension*

Patient No	*Resting electrocardiogram*	*Exercise ST depression (mm)*	*Peak filling rate (EDV/s)*	*Time to peak filling (ms)*	*First one third filling fraction*	*Ejection fraction (%)*	*Wall motion*
3	T-wave inversion LVH						
5					0·13	39	
7		2·5	1·6				
8			1·5				A
9					0·16		
11	T-wave inversion LVH, left axis deviation						A
12	Left axis deviation	3					
17	T-wave flattening				0·15		
18		1·5					
19	LVH and strain	1·5	1·5	330			A
20					0·18		
21	LVH and strain	2	1·0				
22					0·15		A
23					0·17		
24			1·5				
25	Loss of septal R wave	2·5 (pain)			0·15		
27	LVH	3			0·15		A
29		2 (pain)					
30	LVH and strain				0·15		
31					0·18		

LVH, left ventricular hypertrophy, A, abnormal.

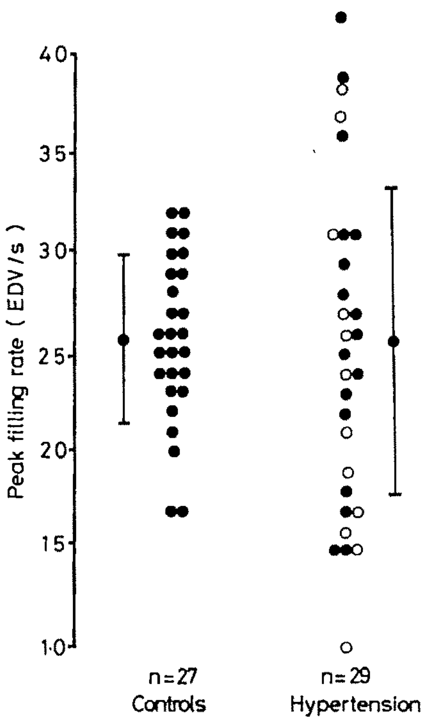

Fig 1 *Comparison of individual peak filling rates (end diastolic volumes per second (EDV/s)) in controls and patients with hypertension with mean (1SD) value shown alongside.* ● = *Normal rest and exercise electrocardiogram;* ○ = *abnormal rest and exercise electrocardiogram.*

filling rate and another two had depression of the first one third filling fraction. Of the five patients with wall motion abnormalities, two had a low peak filling rate and a further two had a low one third filling fraction.

Table 2 lists the mean (SD) of the diastolic measurements of both the subgroups of patients with and without electrocardiographic abnormality, and table 3 shows the results of the comparison with the normal group by unpaired *t* tests.

The one third filling fraction (0·28 (0·16)) was significantly lower in the subgroup of hypertensive patients with a normal electrocardiogram than in the normal group (0·45 (0·16)) ($p < 0·002$). In this subgroup the other two diastolic measurements did not differ significantly from the values in the normal group (tables 2 and 3).

The mean (SD) one third filling fraction in the hypertensive subgroup with electrocardiographic abnormalities was even lower (0·24 (0·09)), and the difference from normal was highly significant ($p < 0·001$). The time to peak filling rate (213 (56) ms) was also significantly longer than in the control group (164 (45) ms) ($p < 0·01$). The peak filling rate of 2·45 (0·78) end diastolic volumes per second was lower than the value of 2·57 (0·42) end diastolic volumes per second in the control group but not significantly.

Because of the different sex ratio between the control group and the patients, we examined the normal subjects for any sex difference between radionuclide measurements. The values of ejection fraction, peak filling rate, and time to peak filling were almost identical in both sexes but the mean first one third filling fraction was 0·376 (0·113) in the 16 women and 0·549 (0·166) in the 11 men. This difference, which was significant ($p < 0·005$) was not related to differences in age, heart rate, or blood pressure between the two sexes.

To explore how the diastolic filling characteristics were influenced by blood pressure and heart rate, each measurement was plotted with the corresponding systolic blood pressure and heart rate measurement. Peak filling rate was strongly correlated with heart rate in the hypertensive patients ($r = 0·60$, $p < 0·001$) but not in the control group. The first one third filling fraction was weakly, negatively cor-

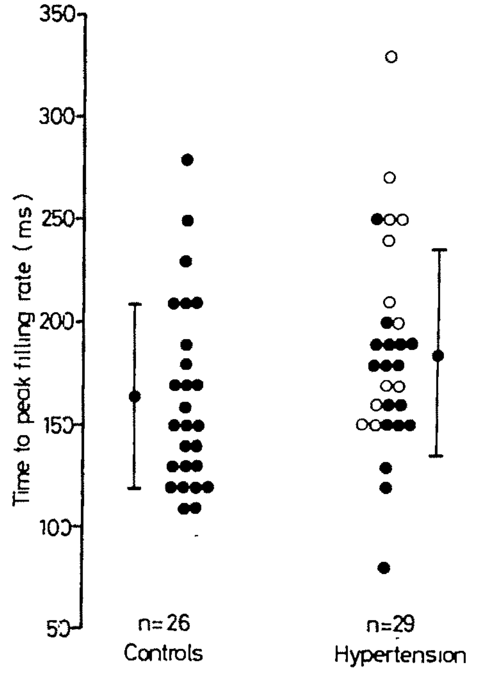

Fig 2 *Time to peak filling in the controls and in patients with hypertension. Mean (1SD) values are also shown.*
● = *Normal rest and exercise electrocardiogram;*
○ = *abnormal rest and exercise electrocardiogram.*

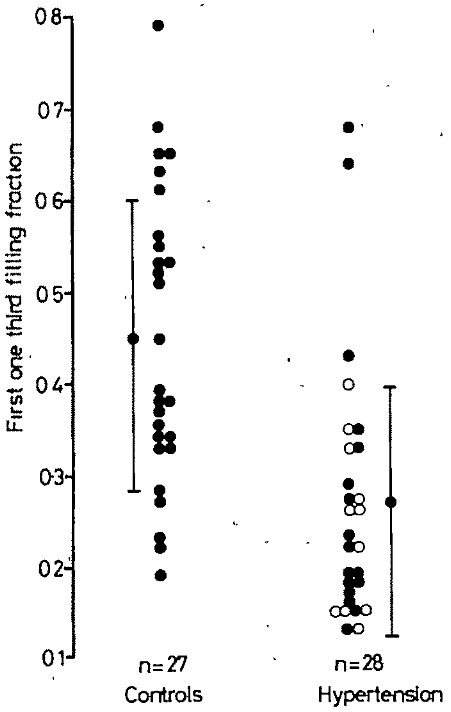

Fig 3 *Comparison of individual first one third filling fractions in controls and patients with essential hypertension. Group mean value (1SD) is shown alongside.*
● = *Normal rest and exercise electrocardiogram;*
○ = *abnormal rest and exercise electrocardiogram.*

related with heart rate in the hypertensive patients ($r = -0.38$, $p < 0.05$) but not in the controls. The time to peak filling rate in the patients with hypertension correlated with systolic blood pressure ($r = 0.52$, $p < 0.005$) but not with heart rate.

At peak exercise the mean (SD) heart rate in the controls was 139·3 (22·3) beats/min and in the hypertensive patients it was 130·9 (19·7) beats/min. This difference was not statistically significant, and there was no significant difference between the exercise time, the peak filling rate, time to peak filling rate, or first one third filling fraction between the two groups at peak exercise. The exercise peak filling rate of the hypertensive patients with a normal electrocardiogram was significantly lower than in the normal group ($p < 0.05$).

Finally, the value of the measurements of exercise diastolic function was examined by dividing those hypertensive patients with normal rest and exercise electrocardiograms according to their ejection fraction response during exercise. Sixteen of these patients had satisfactory exercise studies. In eleven (69%) the ejection fraction during exercise was greater than at rest. In five patients (31%) the ejection fraction fell or remained unchanged at peak exercise. There were no significant differences between any of the measures of diastolic function of these two groups.

Discussion

The results of this study and others suggest that of three diastolic function measurements the first one third filling fraction is the most discriminatory variable for hypertensive patients, both with or without electrocardiographic evidence of ischaemia. There were, however, some noteworthy differences between our study and another study. In the present study, 37% of the patients had a one third filling fraction outside the normal range, compared with 81% of the previously reported patients.[15] The ages of the patients in both studies were comparable, but in the previous study the control subjects were not age matched with the patients and the control group consisted of only 11 healthy men. We found a highly significant difference in the mean one third filling fraction of the 11 male controls and the 16 female controls. This difference could not be accounted for by any age, blood pressure, or heart rate difference. The mean one third filling fraction in these 11 men was 0·55 and Inouye *et al* found a comparable value (0·60) in 11 male controls.[15] Although no sex difference has been found in radionuclide systolic function,[19] it seems that there may be an important sex difference in first one third filling fraction which, to our knowledge, has not been reported previously. This does not weaken the finding that the one third filling fraction, alone of the three diastolic function measurements tested, was abnormally reduced in the hypertensive subgroup with a normal electrocardiogram and normal exercise radionuclide angiography. Balancing the sex distribution of the controls and patients, either by increasing the proportion of men among the controls or by increasing the proportion of women among the patients, would in both instances have tended to exaggerate the difference between the two groups.

The value of the time to peak filling corresponded well with previous reports.[15 20] Although this measurement was not significantly longer in the whole hypertensive group than in the controls, it was significantly longer in the hypertensive subgroup with an abnormal electrocardiogram. Similar prolongation of the time to peak filling has been reported in patients with coronary artery disease,[21 22] so there is a problem of interpreting such findings in patients with hypertension. In an attempt to resolve this we considered the patients with any electrocardiographic or wall motion abnormality as a separate subgroup. There were 12 such patients, 10 (83%) of whom had evidence of myocardial ischaemia as ST segment depression or localised wall motion abnormality. Six had additional evidence of left ventricular hypertrophy on voltage criteria. When this subset of patients with electrocardiographic abnormalities was excluded, the time to peak filling in the remaining hypertensive patients was almost identical to that of the controls. ST segment depression developing during exercise testing in patients with left ventricular hypertrophy does not necessarily indicate obstructive coronary artery disease.[23 24] Presumably "ischaemic" electrocardiographic changes in hypertensive patients with angiographically normal coronary arteries indicate an imbalance between blood supply and demand of the ventricle. Even in the absence of left ventricular hypertrophy, raised systolic blood pressure alone may increase the myocardial oxygen requirement and impair left ventricular coronary reserve.[25]

The statistically significant mean difference between the two observers indicated poor interobserver reproducibility of the time to peak filling. Lack of reproducibility of the same measurement was also found when the nuclear stethoscope was used repeatedly to assess left ventricular function in heart failure.[26] This poor reproducibility was partly explained by difficulty in accurately identifying the end systolic point—this may also have been important in our study, since the hypertensive patients with depressed early diastolic filling tended to have a "flattened" time-activity curve adjacent to the end systolic point. The ejection fraction, filling fraction, and peak filling rate would have been affected less by inaccuracies of end systolic point definition because these measurements were not made exclusively from the time axis of the time-activity curve and whenever a time measurement was used it appeared in the denominator. Other workers have also described wide variations in the measurement of time to peak filling made on two separate occasions.[27]

When others compared radionuclide time to peak filling with the contrast angiography measurement they found a poor agreement.[27] Part of this discrepancy may have been caused by heart rate differences, as the time to peak filling has been reported to be heart rate dependent.[14 15] We found no such association in our study; the measurement was more closely related to systolic blood pressure. Moreover, even when heart rate was fixed by atrial pacing and time to peak filling was compared with a number of haemodynamic variables obtained during cardiac catheterisation, no significant associations were found.[28] For these reasons, the usefulness of this measurement as an early indicator of hypertensive heart disease is open to serious doubt, although the measurement may be a marker for coexistent coronary artery disease. But even this use of the measurement has been questioned.[22]

Our filling rate values corresponded with previously reported figures in hypertension.[14 15] The mean peak filling rate of the hypertensive patients was almost identical to that of the controls. When the subgroup of patients with an abnormal electrocardiogram (who had a mean depressed peak filling rate) was removed, the mean peak filling rate of the remaining hypertensive patients was actually slightly higher than that of the controls. None of these differences was statistically significant. Depression of the peak filling rate has been reported to be an indicator of obstructive coronary artery disease.[21 22 29] On the evidence of the present study, this measurement seemed to contribute little to the early identification of hypertensive heart disease as it was within the normal range in nine (75%) of the patients with an abnormal electrocardiogram.

During exercise the peak filling rate was reduced in the hypertensive patients with a normal electrocardiogram; this difference was just statistically significant ($p < 0.05$) when compared with the controls. The corresponding measurement in the hypertensive group with an abnormal electrocardiogram, however, was not significantly different from normal, even though two thirds of these patients developed electrocardiographic evidence of ischaemia during exercise. This observation is therefore unlikely to be of any clinical importance; this difference with a low level of statistical significance may well have arisen as a consequence of multiple significance testing. All the remaining diastolic function tests failed to discriminate between controls and hypertensive patients at peak exercise. Furthermore, there were no differences between the diastolic measurements when the hypertensive patients with a normal electrocardiogram were subdivided and compared according to the response of their ejection fraction to exercise.

The reason why there was a correlation between some resting diastolic measurements and heart rate and blood pressure in the hypertensive patients but not in the controls may have been because the ranges of diastolic function, heart rate, and blood pressure were wider in the hypertensive group. For example, the heart rate range in the controls was 50–92 beats/min, while in the hypertensives it was 48–130 beats/min. The range of peak filling rate in the hypertensives was 1·5–4·2 end diastolic volumes per second, compared with a range of 1·7–3·2 end diastolic volumes per seond among the controls, and the range of time to peak filling rate was 80–330 ms in the hypertensive patients and 110–280 ms in the normal group. These wider ranges of measurements would have increased the likelihood of any correlations between measurements reaching statistical significance.

In conclusion, the results of this study confirm previous observations that the first one third filling fraction is abnormally low in patients with hypertension, even after the exclusion of those with electrocardiographic evidence of ischaemia or left ventricular hypertrophy. The time to peak filling rate was prolonged in the hypertensive group but this abnormality was confined to those with electrocardiographic abnormalities and may have been caused by coexisting ischaemia. Although the mean peak filling rate was reduced in the hypertensive group with electrocardiographic abnormalities the measurement appeared to be less useful than the electrocardiogram for identifying individuals with cardiac abnormalities since many patients with an abnormal electrocardiogram had normal filling rates despite definite evidence of left ventricular hypertrophy in half of them. The wide normal range of all the diastolic measurements was another indication that they would be of limited use for identifying cardiac abnormalities in individual patients. The effect of treatment on the mean first one third filling fraction in a group of hypertensive patients merits further study.[30] Of the three radionuclide diastolic measurements, only the first one third filling fraction was appreciably different in male and female controls. This new observation requires further investigation with careful control of factors that might affect the measurement, such as the degree of cardiovascular fitness and smoking habits.

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Percutaneous balloon dilatation of calcific aortic valve stenosis: anatomical and haemodynamic evaluation

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SUMMARY Two groups of elderly patients with calcified aortic stenosis were treated by balloon dilatation. In group 1, the valve was dilated just before surgical replacement of the valve. The valvar and annular changes occurring during dilatation were examined visually. In 20 of the 26 patients in this group there was no change. In the six remaining patients mobilisation of friable calcific deposits (1 case), slight tearing of the commissure (4 cases), or tearing of the aortic ring (1 case) were seen. Dilatation did not appear to alter valvar rigidity. In 14 patients (group 2) the haemodynamic gradient across the aortic valve was measured before and immediately after dilatation and one week after the procedure. Dilatation produced an immediate significant decrease of the aortic mean gradient and a significant increase of the aortic valve area. Eight days later the mean gradient had increased and the aortic valve area had decreased. Nevertheless there was a significant difference between the initial gradient and the gradient eight days after dilatation. The initial aortic valve area was also significantly larger than the area eight days after dilatation. The aortic valve gradient rose significantly in the eight days after dilatation and at follow up the gradients were those of severe aortic stenosis.

Percutaneous transluminal balloon dilatation is increasingly used as an alternative to operation to treat arterial stenosis in peripheral, renal, coronary, and supra-aortic circulations.[1-4] There is considerable interest in the long term results of this procedure.[1-4] Percutaneous balloon dilatation was successful in children with stenosis of the pulmonary and aortic valves,[5 6] and transseptal balloon dilatation of the mitral valve was successful in adults.[7-9] More recently Cribier *et al* and McKay *et al* attempted percutaneous balloon dilatation of severe calcified aortic stenosis in elderly patients,[10 11] and the use of this procedure seems to have expanded considerably in the last few months in France where more than 150 patients have undergone percutaneous balloon dilatation of the aortic valve.

We have examined the valvar and annular changes caused by dilatation immediately before the affected valve was replaced in one set of patients and the haemodynamic gradients before and immediately after dilatation and one week after the procedure in another set of patients.

Patients and methods

GROUP 1

Table 1 shows the haemodynamic and anatomical findings in 26 patients who had aortic valve replacement because of a severely calcified aortic stenosis. The procedure was performed as follows: after an extracorporeal circulation and cardioplegia had been established, a transverse aortotomy permitted the examination of the aortic valve, commissures, aortic wall, and calcified deposits. Then a 9Fr balloon catheter (18 or 20 mm diameter when inflated) was introduced through the aortic valve (fig 1). The balloon was inflated several times with 10 ml of saline solution up to a 5 to 6 atmospheres. Then the valve was examined again for tearing of the commissures and valves as well as for any changes in the aortic wall and calcified deposits. Then the aortic valve was replaced by a prosthesis. Several excised aortic valves were submitted to a histological examination. Those aortic leaflets were compared with calcified aortic valves that had not been dilated.

GROUP 2

Table 2 shows the clinical and haemodynamic data in a group of 14 patients who had had percutaneous

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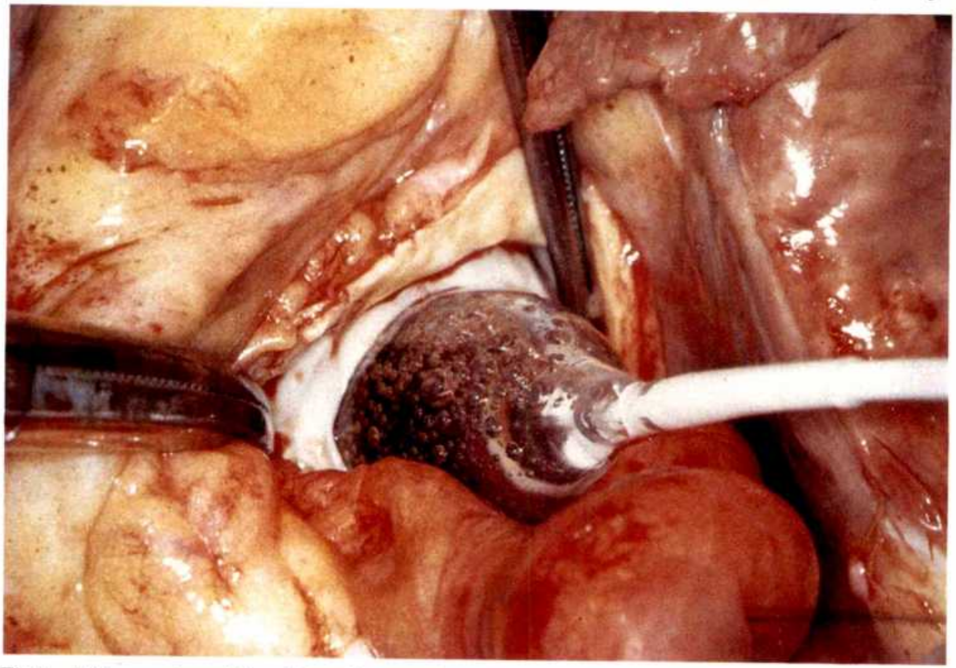

Fig 1 *Balloon catheter inflated through an aortic valve.*

Table 1 *Haemodynamic and anatomical data on patients in group 1*

Case No	*Age and sex*	*LV-Ao mean gradient (mm Hg)**	*AR†*	*Aortic valve*		*Other valve lesions*
				No of cusps	*Commissural fusion‡*	
1	50 M	110	–	2	±	
2	64 M	70	+ +	3	–	
3	61 M	80	+	3	–	
4	50 F	60	+	3	–	MS-TR
5	65 M	75	–	2	–	
6	29 M	100	–	1	–	
7	52 F	60	+ +	3	±	MS + MR + TR
8	66 F	122%	–	3	–	
9	62 M	65	–	2	±	
10	52 M	50	+ +	3	+	MR
11	71 F	131%	+	3	±	
12	53 M	130%	+ +	2	–	
13	77 M	115%	–	2	–	
14	55 F	130%	–	3	+	
15	62 F	60	–	3	±	
16	72 F	110	–	2	–	
17	58 M	75	–	3	–	
18	72 F	50	–	3	–	MS + MR
19	58 M	70	+ +	3	+	MR
20	65 F	118%	–	2	–	
21	59 M	80	+	3	–	
22	74 F	60	–	3	+	
23	59 M	90	+ +	3	+	
24	64 M	50	+	3	–	
25	60 M	60	+ +	2	–	
26	76 M	122%	–	3	–	

*Mean pressure gradient across the aortic valve. When the mean gradient was not measured the corrected left ventricular ejection time (%) was calculated by Meiners method.
†–, No regurgitation; +, slight regurgitation; + +, appreciable regurgitation.
‡–, No fusion; ± slight fusion; + considerable fusion.
AR, aortic regurgitation; MR, mitral regurgitation; MS, mitral stenosis; TR, tricuspid regurgitation.

Table 2 *Clinical and haemodynamic data on patients in group 2*

Case No	*Age and sex*	*Symptoms*	*LV-Ao mean gradient (mm Hg)*	*AR*	*Other valve lesions*	*AVA (cm^2)*	*CO (l/min)*	*Coronary artery luminal narrowing*
1	58 M	Angina, dyspnoea, CHF, syncope	92	+ +	0	0·43	4·9	0
2	74 M	Dyspnoea, CHF	75	0	0	0·29	2·2	
3	73 M	None (bilateral arthritis of the hip)	54	+	0	1·2	7·8	0
4	82 F	Dyspnoea, CHF	123	+	0	0·28	3·2	
5	81 F	Syncope	105	0	MR + +	0·3	3·5	
6	79 F	Angina, dyspnoea	103	+ +	0	0·18	2·7	0
7	64 M	Angina	76	0	0	0·68	5·5	0
8	86 M	Angina, myocardial infarction, dyspnoea, CHF	91	+	MR + +	0·30	3	LAD 50%, RCA 75%; akinesia of posterobasal segment
9	68 M	Angina, dyspnoea	86	+	MR + + TR + +	0·37	4·2	0
10	81 F	Syncope, angina, CHF	81	0	0	0·34	3·2	
11	62 F	Angina, dyspnoea, presyncope	104	+	0	0·38	4·2	0
12	66 F	Dyspnoea	93	0	0	0·39	4·2	0
13	68 M	Dyspnoea, angina	73	+	0	0·31	3·4	CA 90%
14	74 F	Dyspnoea, presyncope	62	0	0	0·32	2·6	0

AVA, aortic valve area; CA, circumflex artery; CO, cardiac output; CHF, congestive heart failure; LAD, left anterior descending artery; RCA, right coronary artery. See footnote to table 1 for other abbreviations.

balloon dilatation of the aortic valve together with catheter studies. All had severe calcified aortic stenosis. In this group the patients preferred a percutaneous attempt to surgical valvar replacement or refused operation. If balloon dilatation was unsuccessful they were offered an aortic valve replacement. Patients gave their informed consent to these procedures.

Cardiac catheterisation

All patients were premedicated with 30 mg of oral diazepam. Right and left sided catheterisation was carried out percutaneously. Right cardiac catheterisation was performed via the left femoral venous approach. In the left cardiac side a 8 Fr pigtail catheter was advanced from the right femoral artery into the left ventricle and another 8 Fr pigtail catheter was introduced through the left femoral artery and was placed in the aortic root to obtain simultaneous aortic and ventricular pressure recordings. Another left ventricular recording was obtained by the transseptal catheter technique with a 8·5 Fr Brockenbrough catheter inserted into the left ventricle through the right femoral vein. The mean aortic valve gradient during the systolic ejection period was obtained by planimetry with the Hewlett Packard catheterisation data analysis system. The mean gradients were calculated first by summing the pressure difference across the valve for each pressure reading obtained while the valve was open and also by dividing this sum by the number of pressure readings. Cardiac output was measured by the thermodilution technique (as the average of three concordant measurements) with a 7·5 Fr Swan-Ganz catheter inserted into the pulmonary artery through the left femoral vein. The aortic valve area was calculated by the Gorlin formula. In all cases coronary arteriography and left ventriculography were performed to assess the severity of coronary lesions and the myocardial function. Moreover, a cineangiogram was obtained of the aortic root and aortic and mitral regurgitation were assessed from 1 to 4+ according to the Grossman criteria.[12] None of our patients had mitral or aortic regurgitation of 3+ or 4+.

Balloon dilatation

The balloon catheter was percutaneously introduced into the right femoral artery on a long guide wire (300 cm long, 0·035 inches diameter); the flexible end was placed in the left ventricular apex to permit the exchange of the pigtail catheter inserted in the left ventricle with the balloon catheter. The balloon catheter was identical to the ones used in the peroperative procedure (9 Fr Mansfield type catheter); diameters of the inflated balloon (18 – 20 mm) were chosen according to the size of the aortic valve annulus as assessed by echocardiography. In all cases only one balloon catheter was used. The balloon catheter was inserted through the aortic valve over the 0·035 inch guide wire that was looped in the left ventricle to stabilise the position of the balloon catheter which otherwise tends to move above or

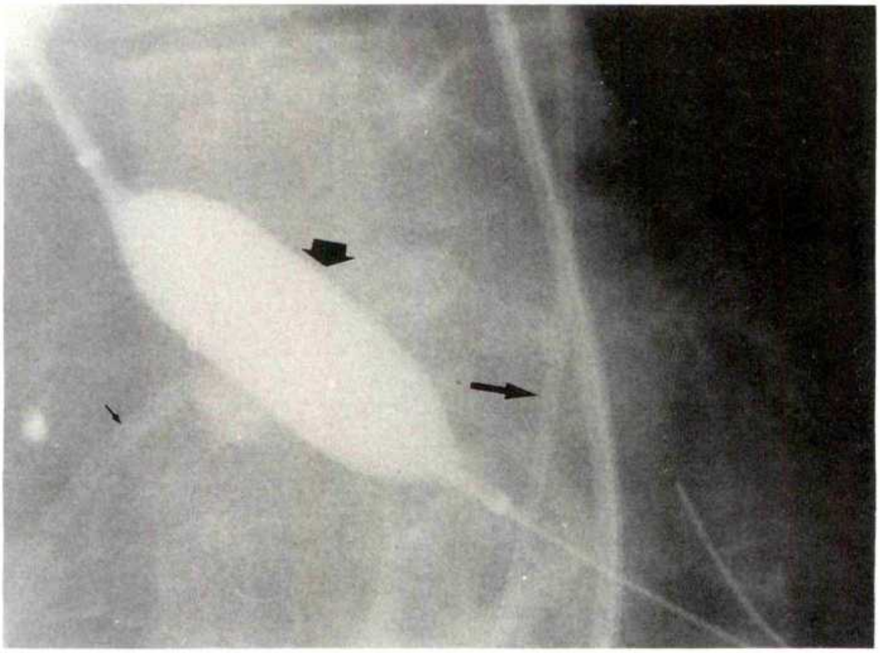

Fig 2 *Cineangiogram of the procedure. The largest arrow shows balloon inflated through a calcified aortic valve; the pigtail catheter for monitoring aortic pressure is shown by the smaller arrow; and the Brockenbrough catheter for left ventricular monitoring is indicated by the smallest arrow.*

below the aortic ring when it is inflated. The balloon catheter was inflated to pressures of 5–6 atm with a 50% mixture of saline solution and contrast medium after appropriate siting of the balloon had been confirmed by the appearance of a waist in the middle of the balloon (fig 2). The inflation-deflation cycle was varied according to the clinical and haemodynamic tolerance. Usually this cycle lasted less than 30 seconds but when the procedure was well tolerated inflation could last two or three minutes. During each inflation simultaneous aortic and ventricular pressures were continuously recorded; the number of inflations was varied according to the clinical tolerance and the decrease in the mean aortic gradient. At the end of the procedure the balloon catheter was withdrawn over the guide wire which was left in place. It was replaced by the pigtail catheter and the new mean aortic valve gradient and cardiac output were measured 20 minutes after the end of the procedure. A series of cineangiograms of the aortic root were examined for evidence of aortic regurgitation. The arterial and venous catheter were removed and haemostasis was achieved by direct compression. After the procedure, patients were monitored in the intensive care unit for one day. During the immediate recovery period 12 patients required a blood transfusion (2–4 units of packed cells). The fall in haematocrit and haemoglobin concentration was not measured.

Haemodynamic follow up: eight days after the procedure a haemodynamic control was carried out through the same technique in the group where a significant gradient decrease had been obtained. This delay was chosen to perform a haemodynamic control during the same hospital stay of our patients. In our group of 14 patients four had no control.

Statistical analysis

Group data are presented as mean (SD); the comparison between the haemodynamic data before, immediately after, and eight days after the procedure were analysed for statistical significance by the Wilcoxon signed rank test used for paired samples. Significance was tested by means of a *t* table.

Results

GROUP 1 (TABLE 3)

In patients with minimal fusion of bicuspid or tricuspid valves only two had 1–2 mm tearing of the commissural fusion (fig 3). The leaflets, aortic annulus, aortic wall, and calcified deposits remained

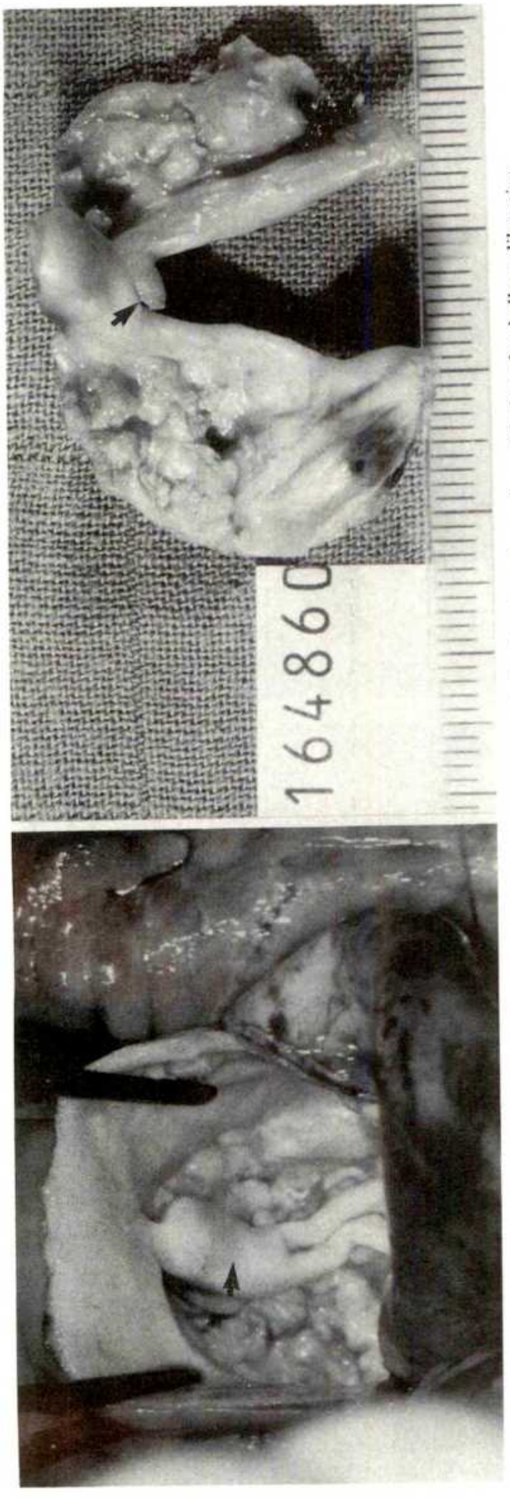

Fig 3 *(Left) Commissural fusion in case 9 before balloon dilatation. (Right) Tearing of commissural fusion after balloon dilatation.*

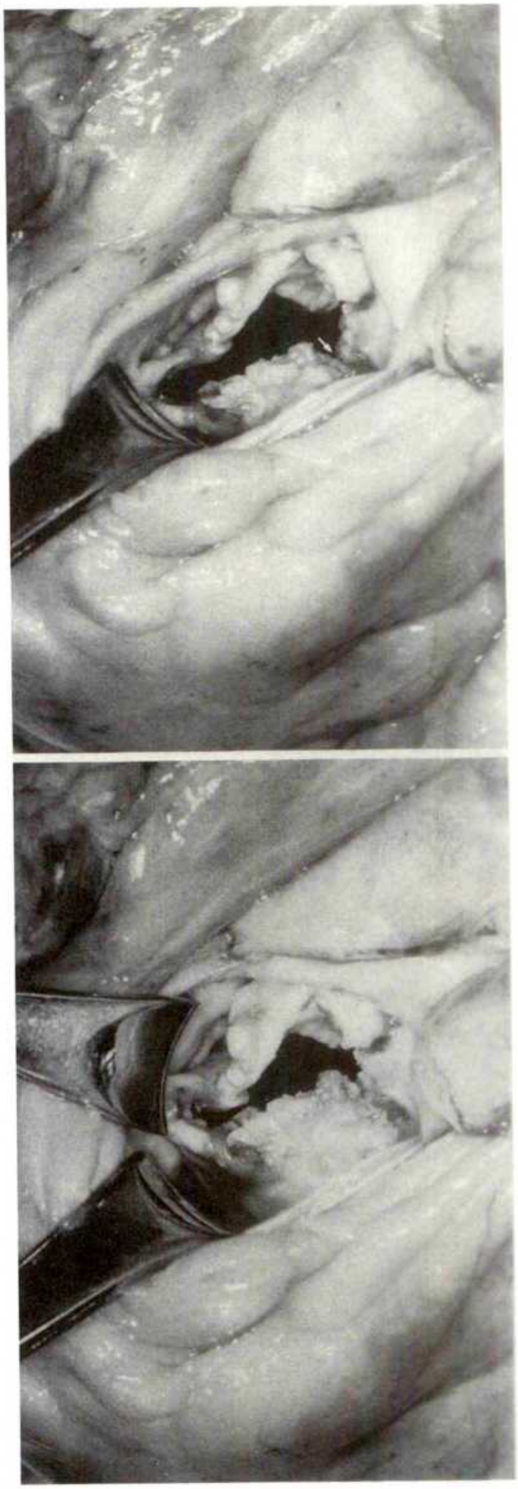

Fig 4 *(a) Aortic valve in case 10 before balloon dilatation. (b) Slight tearing of one fused commissure after dilatation.*

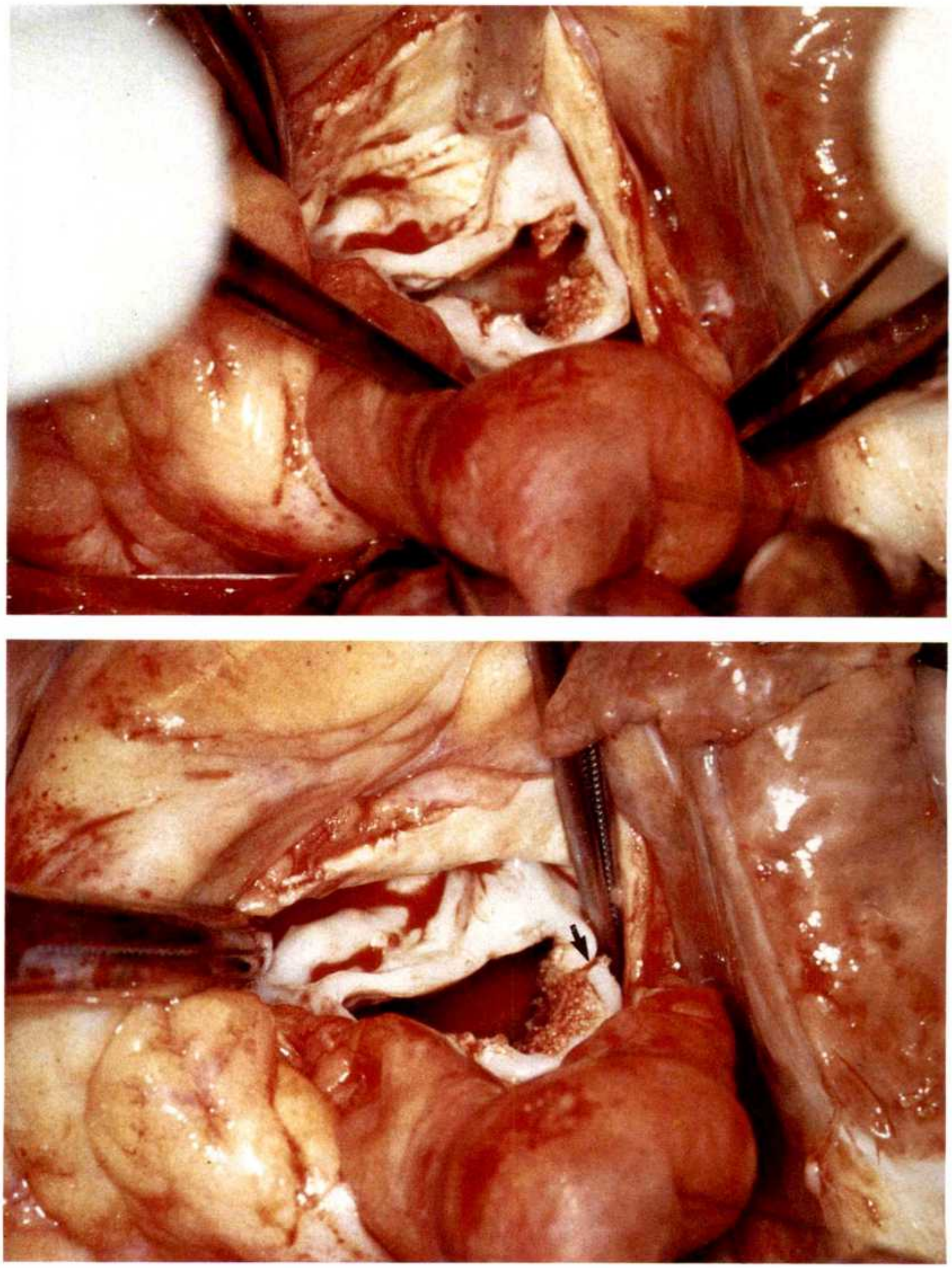

Fig 5 *(Top) Aortic valve in case 19 before balloon dilatation. (Bottom) The arrow shows slight tearing of one fused commissure after dilatation.*

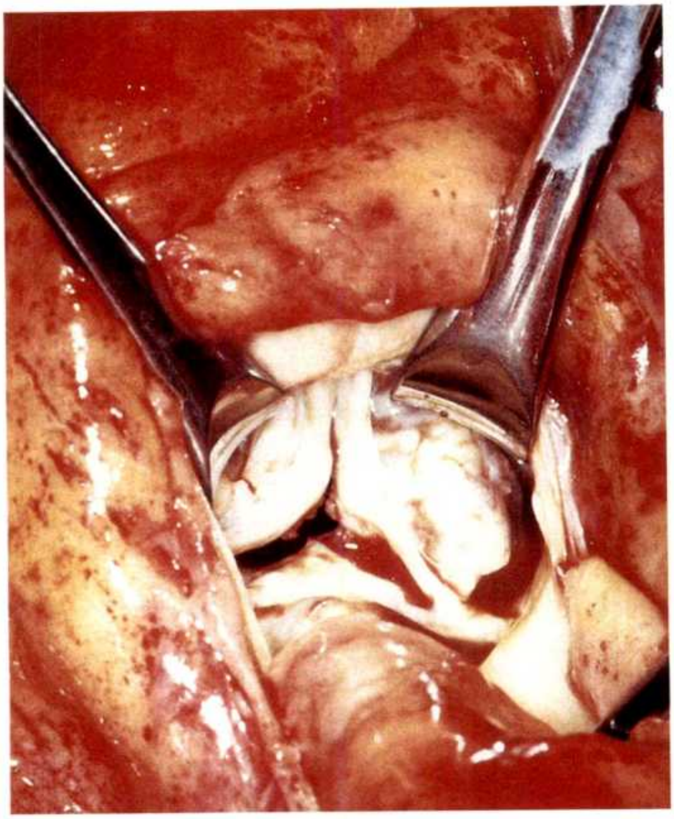

Fig 6 *Peroperative view of the aortic valve of patient 4 (group 2).*

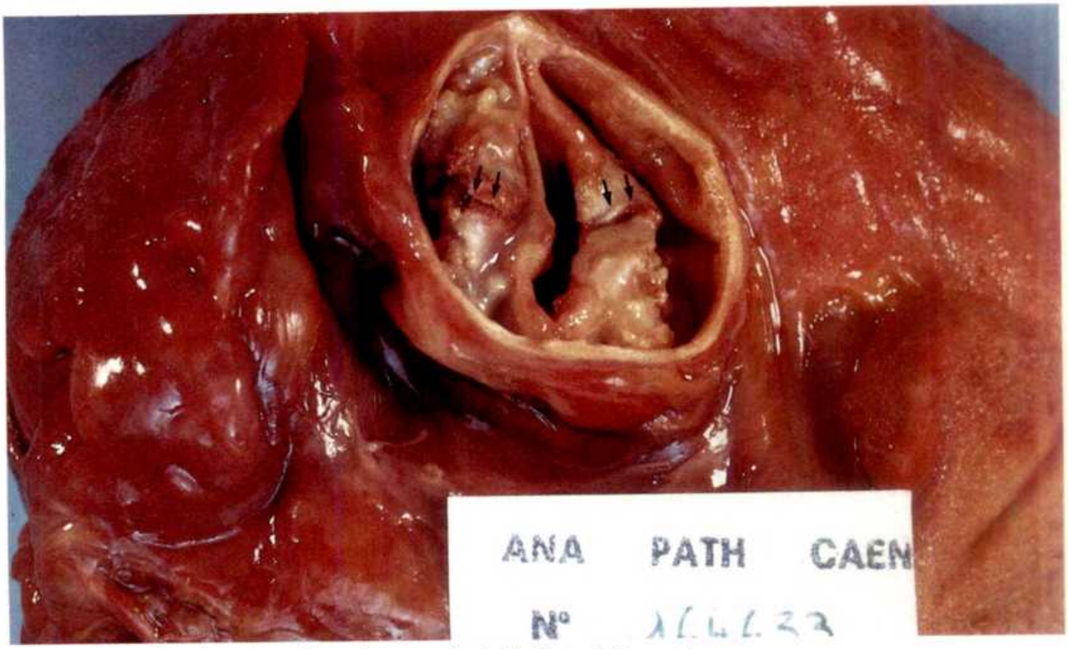

Fig 7 *Bicuspid aortic valve with two fractures of calcified deposits (arrows).*

Table 3 *Anatomical findings in group 1*

Case No	*Valve*	*Macroscopic changes*
9 (fig 3)	Bicuspid with moderate commissural fusion	2 mm tear in commissural fusion
10 (fig 4)	Tricuspid with pronounced bicommissural fusion	2 mm tear in commissural fusion (intercoronary cusp commissure)
14	Tricuspid with bicommissural fusion (one completely fused, other minimally fused)	1mm tear in the smallest commissural fusion
15	Tricuspid with slight fusion of one commissure	Complete tearing of commissural fusion (2 mm)
19 (fig 5)	Tricuspid with considerable fusion of three commissures	Slight tearing
22	Tricuspid with complete fusion of one commissure	Slight tearing of aortic annulus

unchanged. In valves with more appreciable commissural fusion or an uncertain structure there were three instances of 1–2 mm tears of the commissural fusion (figs 4 and 5). In one case there was a 1 mm tear of the aortic ring. In the 20 other patients there was no evidence of any change. In one case the introduction of the balloon catheter through the valve mobilised the friable calcified deposits on the free edge of a hemi-valve. Balloon dilatation did not appear to change the valve rigidity.

GROUP 2

Clinical follow up

Four patients were not followed up after dilatation. Patient 5 died two days after the procedure in intractable cardiac failure after the onset of tachycardia despite an immediate decrease of 20 mm Hg of the mean valve gradient after dilatation. Patient 1 was operated on after the relative failure of the initial procedure; his aortic valve was tricuspid and showed neither commissural fusion nor leaflet tearing. Patient 3 refused follow up catheterisation; a bilateral hips operation was planned two months later but tachycardia prevented this. His haemodynamic condition is stable but his physical activity is limited. In patient 11 percutaneous balloon dilatation of the aortic valve was stopped after the first inflation caused syncope because of hypotension. When the aortic valve was replaced it was found to be tricuspid with a tricommissural fusion; the cusps were heavily calcified and the aortic orifice was fixed; there was neither tearing nor fracture of the commissures. These features suggested rheumatic disease of the valve. Ten patients had a follow up catheter study to assess haemodynamic function. Patients 2, 7, and 10 refused aortic valve replacement which was recommended after percutaneous balloon dilatation had failed to improve their condition. Their clinical condition remained stable (New York Heart Association functional class III or IV) for three months, two months, and one and a half months after the dilatation. Patient 4 was clinically improved after balloon dilatation but had bilateral pleural effusion drainage. A worsening of symptoms three weeks later led to operation. The aortic valve was tricuspid, heavily calcified with slight commissural fusion. No changes attributable to the balloon dilatation, such as tearing of the commissures or disruption of calcified deposits were noted (fig 6). Although the mean gradient in patient 8 did not increase again after dilatation he was not clinically improved and later required valve replacement. His excised aortic valve was tricuspid with no commissural fusion. The three cusps and the calcified deposits showed neither rupture nor injury. In patient 9 the mean gradient across the aortic valve only rose slightly after dilatation but he was not clinically improved. He had an aortic valve replacement and a tricuspid valve annuloplasty. The aortic valve was tricuspid with no commissural fusion. The leaflets were heavily calcified; there was no fracture of either the calcified deposits or the cusps. Despite a final decrease of 25 mm Hg in the mean aortic gradient patient 6 died of refractory congestive heart failure one and a half months after dilatation. Necropsy showed major left ventricular hypertrophy and a bicuspid aortic valve (fig 7); this valve was rigid and with heavy calcification of the raphe. On each commissure there was a large broken calcified deposit. Each fracture was 0·5 cm long and 0·3 cm deep. In spite of these changes the valve could not be mobilised with the fingers. Stenosis in this case seemed to be caused by the rigidity of the cusps. Patient 14 had only a two week clinical follow up: dyspnoea lessened; the control mean gradient was less than 40 mm Hg but the aortic value orifice was considerably reduced because the cardiac output remained low.

HAEMODYNAMIC RESULTS (TABLE 4)

There was an immediate decrease in the mean aortic gradient in all patients after dilatation, but in nine of the 10 patients who were followed up eight days later this gradient subsequently increased. In two cases

Table 4 *Haemodynamic results in group 2*

	Before			*After*			*8 days after*		
Case No	*LV-Ao (mm Hg)*	*AVA (cm²)*	*CO (l/min)*	*LV-Ao (mm Hg)*	*AVA (cm²)*	*CO (l/min)*	*LV-Ao (mm Hg)*	*AVA (cm²)*	*CO (l/min)*
1	92	0·43	4·9	89	0·44	4·9			
2	75	0·29	2·2	35	0·51	1·9	76	0·31	2·7
3	54	1·20	7·8	31	1·50	7·9			
4	123	0·28	3·2	56	0·41	3·0	112	0·27	3·1
5	105	0·30	3·5	86	0·38	3·5			
6	103	0·18	2·7	53	0·21	1·9	78	0·25	3·2
7	76	0·68	5·5	45	0·80	4·8	56	0·78	5·7
8	91	0·30	3·0	76	0·35	3·2	73	0·48	4·1
9	86	0·37	4·2	45	0·71	4·5	74	0·38	3·8
10	81	0·34	3·2	5	1·53	3·6	60	0·47	3·8
11	104	0·38	4·2	97	0·31	4·1			
12	93	0·39	4·2	39	0·63	3·2	75	0·48	4·2
13	73	0·31	3·4	44	0·41	2·7	57	0·67	4·8
14	62	0·32	2·6	36	0·25	1·3	39	0·21	1·3

this increase was slight (fig 8). In 11 patients there was an increase in the area of the aortic valve orifice immediately after dilatation. In seven of the 10 patients who were followed up the area had decreased (fig 9). Immediately after balloon dilatation the mean aortic gradient fell significantly ($p < 0·01$) and the aortic valve area increased significantly ($p < 0·01$) but eight days after dilatation the mean gradient had risen and the aortic valve area had become smaller. Nevertheless, the difference between the initial and follow up gradients was significant ($p < 0·01$), as was the difference between aortic valve areas ($p < 0·05$). The gradient across the aortic valve increased significantly in the eight days after dilatation ($p < 0·01$) but there was no significant change in cardiac output (table 5). Moreover, in one patient who had aortic regurgitation before dilatation cineangiograms obtained after the procedure showed an increase in regurgitation (from 1+ to 2+). Patients without aortic regurgitation did not have regurgitation after the procedure.

The Gorlin formula[13] does not always give an accurate approximation of the actual valve area. This formula considers a fixed valve area and a steady blood flow. Moreover, empirical constants are used. Further error was introduced in the original formula by assuming that the left ventricular mean diastolic pressure was 5 mm Hg. Also the large variations in

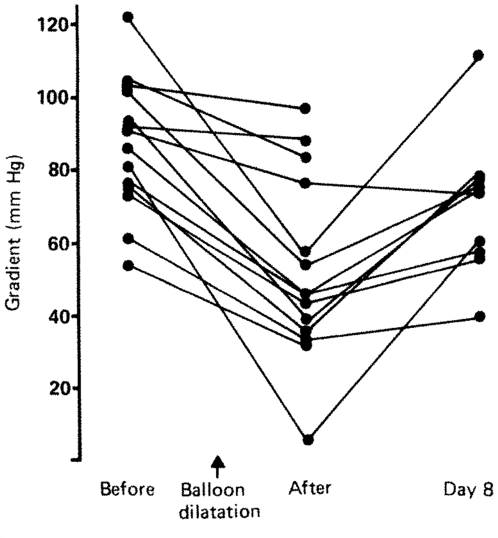

Fig 8 *Changes in aortic mean gradient immediately after dilatation and eight days later.*

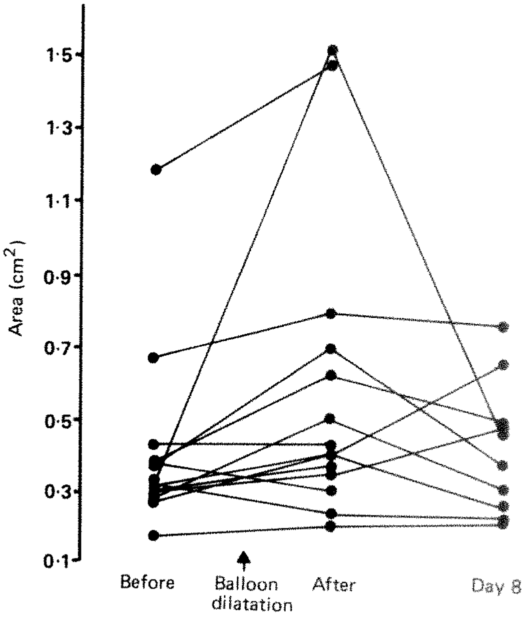

Fig 9 *Changes in aortic valve area immediately after dilatation and eight days later.*

Table 5 *Statistical analysis of haemodynamic results in group 2*

		Before (mean(SD))	*After (mean(SD))*	*8 days after (mean(SD))*
		▼ ———— *	———— ▼	
LV-Ao (mm Hg):	All patients	87·0 (18·5)	52·6 (25·8)	
			▼ ———— *	———— ▼
	Follow up group	86·3 (17·4)	43·4 (18·1)	70·0 (19·3)
		▲ ———— *	———— ▲	
		▲ ————	———— * ————	▲
AVA (cm²):	All patients	0·41 (0·25)	0·60 (0·42)	
		▲ ———— *	———— ▲	
			▼ ———— ***	———— ▼
	Follow up group	0·35 (0·13)	0·58 (0·38)	0·43 (0·18)
		▲ ———— *	———— ▲	
		▲ ————	———— ** ————	▲
CO (l/min)	All patients	3·9 (1·5)	3·60 (1·6)	
		▲ ———— ***	———— ▲	
	Follow up group	3·4 (1·0)	3·01 (1·1)	3·7 (1·2)
		▲ ———— ***	———— ▲	
		▲ ————	———— *** ————	▲

*p ⩽0·01; **p ⩽0·05; ***NS.
See footnote to tables 1 and 2 for abbreviations.

flow pattern across the calcified aortic valve may alter the relation between the orifice area and pressure gradient. Therefore, estimation of valve areas, particularly at low flow rates, may be incorrect and should be regarded as measurements of functional size.

HISTOLOGICAL FINDINGS

A pathologist examined the aortic valves from two patients (cases 6 and 9). Patient 6 had an unicommissural valve that was 3 cm diameter and 0·7 cm thick. It was irregularly thickened and rigid with important calcified deposits over the whole valve (leaflets, free edge, annulus). The valve was composed of fibrous, dense, acellular, sometimes hyaline tissue and included calcified deposits of unequal sizes, frequently surrounded by macrophagic granulomas with some giant cells. The endothelium was histologically unchanged. There were no macroscopic or histological changes attributable to balloon dilatation. Patient 9 had a bicuspid valve that was 3·5 cm along its longest axis, 2·4 cm along its shortest axis, and 0·5

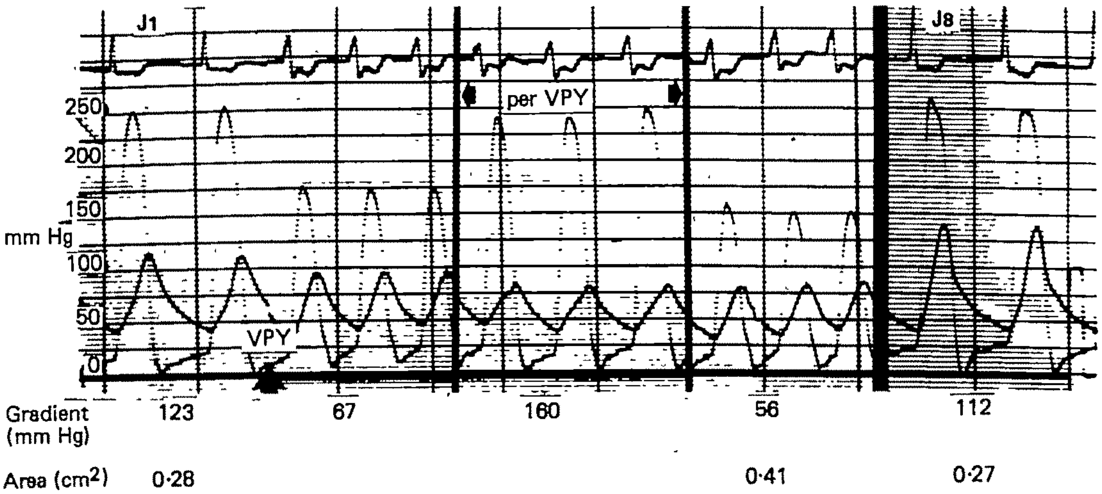

Fig 10 *Simultaneous recording of left ventricular and aortic pressures before, during, and after balloon dilatation in case 4 (group 2). There were ischaemic changes on the electrocardiogram and the mean gradient pressure increased during dilatation.*

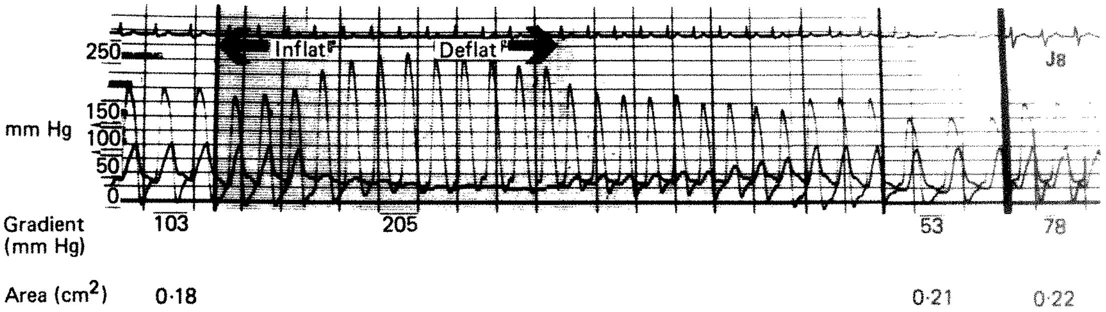

Fig 11 *Simultaneous recording of left ventricular and aortic pressures before, during, and after ballon dilatation in case 6 (group 2). There was a considerable increase in mean gradient pressure during dilatation.*

cm deep. The valve structures were heavily and irregularly calcified. The commissures and free wall were thickened and rigid but the fusion was minimal and measured 1 cm on its anterior tip. This fusion was torn for 2 mm, probably by the balloon dilatation. The valve was made up of fibrous and hyaline tissue and contained few vessels. There were irregular calcified bodies that did not contain macrophages. No histological or macroscopic abnormalities that were attributable to the balloon dilatation were seen.

The pathogist also examined the aortic valve from patient 6 in group 2. The valve structures were thickened by dense and hyaline fibrosis and a large calcified mass, which in places showed osteoid metaplasis. Apart from the two splits described above, fissure and splitting caused by balloon dilatation were not seen.

Discussion

Like other workers we found that most elderly patients with calcified stenosis of the aortic valves have either tricuspid aortic valves with no or few commissural fusions (Monckeberg disease) or bicuspid valves.[14-16] The stenosis and the haemodynamic gradient were more the result of rigid, stiff aortic valves with heavily calcified cusps than of a fixed anatomical stenosis caused by commissural fusion. We found that inflation of the balloon during dilatation raised the aortic cusps because of the pressure exerted on the endoventricular side of the cusps. We saw no fracturing or tearing of calcified deposits. During deflation of the balloon the aortic cusps returned to their initial position with no apparent change in their rigidity. In cases in which the structure of the valve was uncertain and there was commissural fusion balloon inflation did produce a slight tearing. But in our opinion this could not account for any benefit or long term success. Balloon dilatation is also unlikely to tear the aortic annulus. In this group there were no appreciable macroscopic changes to the aortic valves, more specifically we did not see fissuring or fragmentation of the calcified deposits.

Although there was a real and significant fall in mean aortic gradient immediately after balloon dilatation, this did not persist and eight days after the procedure, despite a significant decrease in the mean aortic gradient and significant increase of the valve area when compared with the valves before dilatation, the haemodynamic valves remained within the range for severe aortic stenosis.

We believe that the immediate fall and secondary rise in the mean aortic gradients are explained by the important blood loss associated with the procedure and also arrhythmia and transient ischaemia that occur during the procedure. Twelve of our patients required transfusion in the immediate recovery period. These postcharge increase and myocardial ischaemia (secondary to the partial occlusion of the coronary ostia by the calcific aortic leaflets during the balloon inflation) are performed on hypertrophic and failing hearts.

We believe that the indication most favourable for percutaneous aortic dilatation is stenosis caused by symmetrical commissural fusion of a tricuspid uncalcified valve such as that associated with rheumatic disease. None of our patients, however, had valves like this, and aortic stenosis in elderly patients is rarely caused by rheumatic disease.[14] Furthermore, 90% of elderly patients with pure aortic stenosis have a tricuspid valve; $\leqslant 30\%$ have fusion of one or two of the commissures and fusion of all three commissures is exceptional.

We believe that percutaneous balloon dilatation of the aortic valve in elderly patients is seldom helpful. But any benefit of the procedure in elderly patients with severe aortic stenosis can only be assessed by clinical follow up and multicentre short term and long term studies of haemodynamic function and morbidity and mortality.

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Arrival-time analysis of intravenous digital aortograms in aortic dissection

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SUMMARY Arrival-time analysis was applied to intravenous digital aortograms. A single static image was produced by representing the time to 90% maximum density for each image pixel on a grey scale. Arrival-time analysis confirmed the diagnosis in four of six patients with aortic dissection that had been shown by image subtraction. In a further three patients with no dissection the arrival-time images were normal. In two patients with surgical repair of the ascending aorta, residual false lumens were shown by both subtraction and arrival-time analysis. In one of these cases arrival-time analysis prompted reanalysis of the subtraction image that had previously been interpreted as showing a normal aorta.

Arrival-time analysis provides a static image of aortic dissection, which helps to overcome subtraction artefact.

We have already shown the value of intravenous digital subtraction aortography in the diagnosis of acute aortic dissection.[1] We found that this technique was as specific and sensitive as direct cineaortography. Careful interpretation of the images is essential to prevent overdiagnosis of dissection through misinterpretation of linear subtraction artefacts as being the intimal dissection flap, particularly when static images are studied. This problem can be overcome by acquiring images at a rapid frame rate and by viewing the whole sequence. This will detect the characteristic motion of the dissection flap throughout the cardiac cycle. Subtraction artefacts can be abolished by the development of analysis techniques that do not require image subtraction.

We have therefore developed computer software to produce arrival-time images of the aorta. These have the advantage of avoiding image subtraction, and thus permit an assessment of a complete time series of images in one static image. Used in combination with digital subtraction they should give more accurate diagnoses.

Patients and methods

To evaluate arrival-time imaging in the diagnosis of aortic dissection we reassessed several intravenous digital aortograms from our magnetic tape database. These included data from seven out of 11 patients who have been reported elsewhere[1]; data from the remaining four cases were not available on tape. All seven patients had presented with a clinical diagnosis of suspected acute aortic dissection. In three, digital subtraction had shown a dissection of the ascending aorta and this had been confirmed at operation. In one case the subtraction images had demonstrated dissection confined to the descending aorta, and this had been confirmed by cineangiography; operation was not undertaken. In three cases, no dissection had been seen either on the digital subtraction aortograms or at direct cineaortography.

We also analysed data from patients examined after the publication of our previous report. In two patients digital subtraction showed a chronic dissection of the ascending aorta, and this was confirmed by cineangiography in both cases and at operation in one. Postoperative data from two patients were also analysed by arrival-time processing. In one case the ascending aorta had been replaced and the investigation was performed to assess the extent of the residual dissection. A dissection extending from a point just distal to the left subclavian artery down to the aortic bifurcation was seen on the subtraction images. In the second case arrival-time analysis was performed at the time of the initial digital aortogram. The ascending aorta

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had been repaired with a sleeve of Dacron, and the digital investigation was performed because a small bulge was seen on the right side of the ascending aorta on a conventional chest *x* ray.

Intravenous digital aortography was performed as described elsewhere.[1] The digital system used was the Siemens Digitron 2 connected on-line to a standard Siemens Angioskop system. Digital aortograms were performed by pulsed radiography at 12·5 frames/second and displayed on a 256 × 256 matrix. Angiography was performed percutaneously via the antecubital or femoral vein with a 5 French Cordis Superflow pigtail catheter positioned in the right atrium to achieve a central injection of contrast medium. A 30° or 60° left anterior oblique projection was used; in some cases both projections were used if image quality and patient compliance were poor. Images were acquired over a 10 second period after a bolus injection of 40 ml iohexol at 20 ml/s with a 5 s delay to allow for pulmonary transit.

The resultant images were then examined by arrival-time analysis as follows. The maximum and minimum densities throughout the image time series were determined for each image pixel. The time from the start of the series to 90% maximal density of each pixel (the arrival-time) was then determined (fig 1). A single static image was produced, each image pixel being represented on a grey scale according to its arrival-time—early arrival was light and late arrival was dark. The resultant images were then compared with the standard subtraction images to assist in the accurate diagnosis of aortic dissection.

Results

In four of the six patients with known dissection, the arrival-time images clearly demonstrated the true and false lumens by a difference in arrival-time (figs 2 and 3). All these dissections were in the ascending aorta and the delayed arrival that represented the false lumen was seen on the right-anterior aspect of the aorta in all cases. In two of these four cases a gradation of arrival-time was seen in the false lumen, with the earliest arrival occurring just proximal to the innominate artery in one case and just distal to the left subclavian in the second case. At operation the entry site of the dissection was in the ascending aorta well above the coronary orifices in the first case and no entry site was found in the ascending aorta in the second case, indicating that it was distal to the left subclavian artery. In the other two cases arrival-time analysis showed that the false lumen extended into the innominate artery.

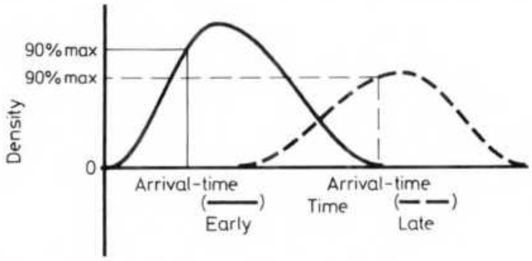

Fig 1 *Time-density curves for two image pixels demonstrating the method of measuring arrival-time.*

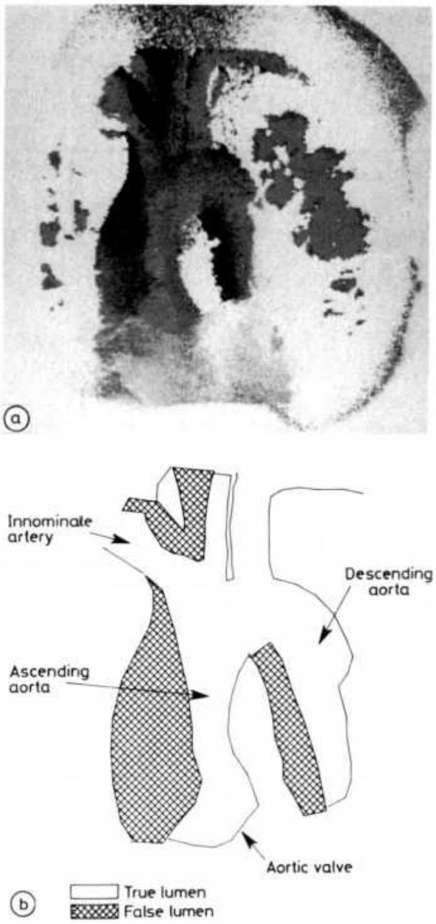

Fig 2 *Arrival-time image (a) showing a dissection of the aorta extending from the aortic valve into the innominate artery and the descending aorta. (b) Explanatory diagram.*

In two patients, one with dissection of the ascending aorta and the other with dissection of the descending aorta, no dissection was seen on the arrival-time images. When the subtraction images were reviewed in these two cases multiple linear

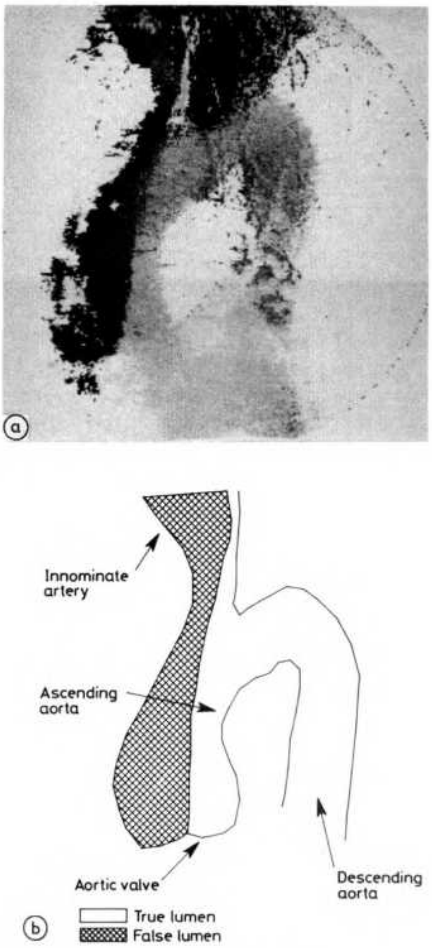

Fig 3 *Arrival-time image (a) showing dissection of the aorta extending from the aortic valve into the innominate artery. (b) Explanatory diagram.*

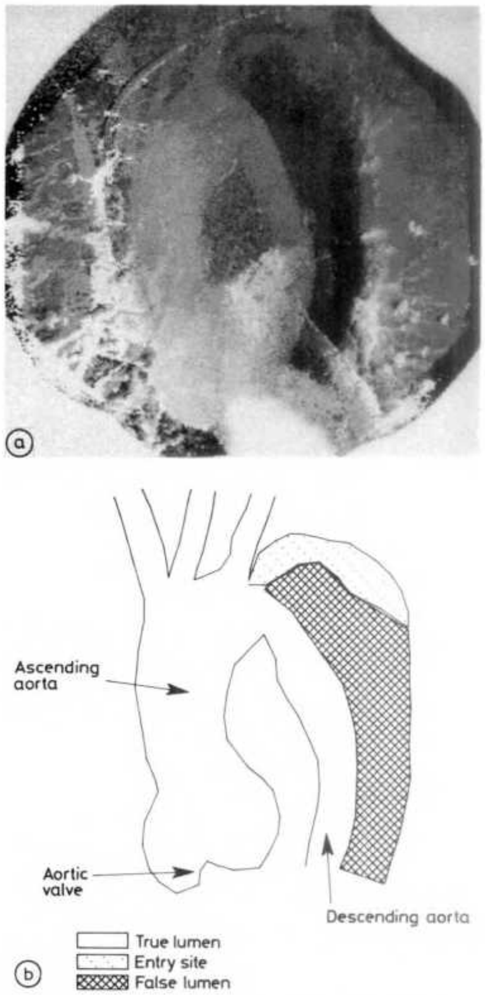

Fig 4 *Arrival-time image (a) showing a residual false lumen in the descending aorta after repair of the ascending aorta. (b) Explanatory diagram. Early enhancement by contrast showed that the entry site of the false lumen was just below the left subclavian artery.*

opacities were apparent, suggesting severe disruption of the intimal flap, such that the true and false lumens filled simultaneously.

In the three patients previously shown both by subtraction and by conventional cineaortography to have no dissection the arrival-time images demonstrated the expected pattern of contrast distribution throughout the aorta with a progressive delay in arrival-time throughout the length of the aorta.

Two patients were studied after operation. In the first the presence of a dissection extending from a point just distal to the left subclavian artery down to the aortic bifurcation was confirmed by the arrival-time image in which the false lumen was clearly demonstrated by a delay in arrival-time (fig 4). The contrast first arrived in the false lumen at the level of the left subclavian artery, with progressive delay in arrival-time along the length of the descending aorta. In the second patient digital investigation was performed to determine the nature of a small bulge on the right side of the aorta and the ascending aorta was initially thought to be normal on the subtraction images. There was a considerable delay in arrival-time in a small area in the right-anterior aspect of the aorta, corresponding to the bulge on the chest *x* ray, and this drew attention to a small leak of contrast

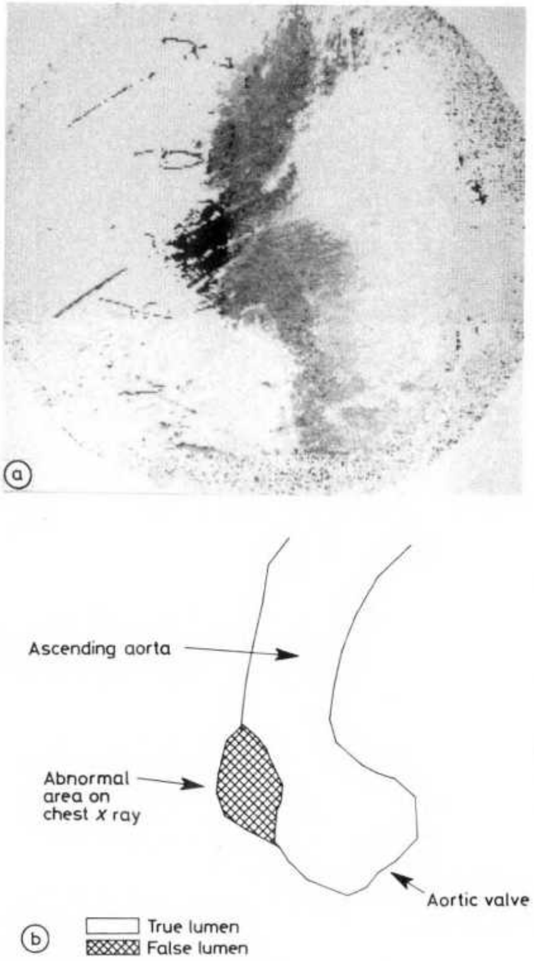

Fig 5 *Arrival-time image (a) in a patient after operation. There is a small leak of contrast medium around the Dacron sleeve in the ascending aorta. (b) Explanatory diagram.*

medium into a false lumen at the site of the proximal anastomosis (fig 5). This finding was subsequently confirmed by conventional cineaortography.

Discussion

The thoracic aorta is very suitable for investigation by intravenous digital angiography[2] because it is relatively immobile and the images do not require a high degree of spatial resolution or contrast density. We found that digital subtraction was as accurate as cineaortography in the diagnosis of aortic dissection.[1] But the possibility of mistaking a subtraction artefact for an intimal dissection flap has led to efforts to develop analysis methods that do not depend on image subtraction. One such technique is arrival-time imaging.[3]

In pixels that are enhanced by the arrival of contrast medium the shade of that pixel in the arrival-time image will be determined by the time taken for contrast to reach that pixel and also by the time taken for that pixel to be maximally enhanced by contrast. Thus it is possible to distinguish two lumens even if contrast enters simultaneously, provided the rate of flow in the two lumens is different.

In pixels that are not enhanced by contrast there should be little variation between the maximum and minimum values. But all pixels will vary slightly, in random fashion, and therefore the arrival-time of the background structures should be random. In practice, however, random variation in the background is masked by the effect of *x* ray scatter. *X* ray scatter varies with the overall density of the structure under investigation; the greater the density the greater the scatter. Therefore as contrast medium arrives in the structure under study the degree of background scatter will increase. This will have the effect of reducing the background image density, and hence the pixel density. This means that background image pixels will achieve maximal density very early in the study, and this area will be represented as having a very early arrival-time. It would be possible to prevent this effect by correcting the images for variation in *x* ray scatter. This is not necessary, however, as the very early arrival-time of the background structures enables them to be distinguished from the contrast enhanced structures.

The diagnosis of aortic dissection by arrival-time imaging of the thoracic aorta is dependent on the fact that contrast enhancement usually occurs later in the false lumen than in the true lumen. Thus these two lumens can be distinguished by a difference in arrival-time which is represented on the images as a difference in grey scale. This was found to be the case in four of the six patients with known aortic dissection, and in the patient in whom a residual descending dissection was found after operation. Furthermore, the site of entry of the dissection in the three patients with distal entry sites could be identified from the pattern of arrival-time throughout the false lumen. In two patients the subtraction images showed severe disruption of the intimal flap and no difference in flow could be seen between the true and false lumens. It is therefore not surprising that arrival-time imaging was unable to detect dissection in these patients. The arrival-time images were normal in three patients in whom dissection had been excluded both by subtraction and by cineaortography.

In one case the arrival-time image helped in the interpretation of the subtraction aortogram. In this patient the subtraction images after operation were initially assessed as normal. When an arrival-time delay to the right-anterior aspect of the aortic root was demonstrated, however, it prompted reassessment of the subtraction images. A very faint image of contrast medium leaking into a false lumen was now seen. This illustrates another advantage of this technique—because the analysis is dependent on the maximal density of each pixel and not on the absolute pixel density, a minor degree of contrast enhancement will be detected to the same extent as considerable enhancement. Thus attention may be drawn to a false lumen which may not be noticed on the initial subtraction images.

Because analysis of arrival-time imaging throughout the whole time series is obviously subject to sideways motion it therefore has a lower spatial resolution than subtraction imaging. Sideways motion can also produce unexpected arrival-times at the edges of structures under study. So such images should be studied in conjunction with the subtraction images; thus a combination of the techniques may provide more information than either study alone.

In this series aortic dissection could readily be diagnosed from the subtraction images alone. In one patient, however, the diagnostic accuracy of the subtraction images was improved by the arrival-time image. In the other patients the arrival-time images confirmed the diagnosis. Thus this method of arrival-time analysis, when used in conjunction with the subtraction images, assists in the exclusion of subtraction artefact, and furthermore produces one static image of a whole time-series of images. We are studying a larger number of patients to determine whether arrival-time analysis should be recommended as a routine adjunct to digital subtraction aortography.

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Classification of hypertrophied hearts in essential hypertension: evaluation by left ventricular wall stress and adrenergic responses

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SUMMARY Left ventricular mass, fractional shortening, and end systolic wall stress (mechanical indices) measured by echocardiography and the response of fractional shortening and end systolic wall stress to the infusion of isoproterenol (0·02 μg/kg/min for 5 min) (a non-mechanical index) were studied in 57 patients (mean (SD) age 49(8)) with essential hypertension. Nineteen patients had subnormal end systolic wall stress (group 1), 25 patients had normal end systolic wall stress and slightly increased left ventricular mass (group 2A), and 13 patients had normal end systolic wall stress and considerably increased left ventricular mass (group 2B). Plasma noradrenaline concentration was higher in group 2B than in the other groups. When end systolic wall stress was >12 g/cm^2 this variable showed a significant inverse linear relation with fractional shortening before isoproterenol infusion. The inotropic response to isoproterenol was measured as the increase of fractional shortening corrected for the decrease of end systolic wall stress ($\triangle$ fractional shortening/ $-\triangle$ end systolic wall stress). The mean (SD) change in $\triangle$ fractional shortening/ $-\triangle$ end systolic wall stress was significantly larger in group 1 (1·40 (0·60) cm^2/g) than in group 2A (0·85 (0·39) cm^2/g), and was significantly larger in group 2A than in group 2B (0·56 (0·15) cm^2/g).

In patients with hypertensive hypertrophy with subnormal end systolic wall stress (inappropriate hypertrophy) the β adrenergic response is increased; in hypertensive hypertrophy with normal end systolic wall stress (appropriate hypertrophy), however, it is normal, or becomes reduced as plasma noradrenaline increases.

When left ventricular pressure is excessive the left ventricle becomes hypertrophied in an attempt to reduce left ventricular systolic wall stress. The hypertrophy results in left ventricular dysfunction. The way that the grade of hypertension, the extent of hypertrophy, and the severity of left ventricular functional abnormalities interact has not been established.

Several investigators have shown that adrenergic factors can cause cardiac hypertrophy to develop in laboratory animals.[1 2] These results remain controversial and this effect has not been investigated in human hypertension.

We have attempted to classify clinical hypertensive hypertrophy on the basis of its mechanical (left ventricular systolic wall stress) and non-mechanical effects (adrenergic response).

Patients and methods

PATIENTS

We studied 57 hypertensive patients with left ventricular hypertrophy who had had hypertension for > five years. We measured blood pressure by cuff sphygmomanometer, using phases 1 and 5 of the Korotkoff sounds. Arterial hypertension was defined as persistent systolic arterial pressure > 150 mm Hg or diastolic arterial pressure > 95 mm Hg before antihypertensive treatment was started or four weeks

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after the discontinuation of antihypertensive drugs. Essential hypertension was diagnosed in all 57 patients and all of them had echocardiographic evidence of left ventricular hypertrophy: (*a*) interventricular septal wall thickness of ≥12 mm at end diastole, (*b*) left ventricular end diastolic posterior wall thickness of ≥12 mm, and (*c*) left ventricular mass greater than 2 SD deviations above the normal mean. To restrict the study to patients with pure hypertrophy we studied only those with a left ventricular end diastolic diameter of < 55 mm (46 men and 11 women aged 43–68). None of these patients had evidence of other heart disease from their cardiovascular history, or from physical examination, electrocardiography, or echocardiography; and they were all in sinus rhythm without signs of heart failure. Because coronary arteriography was not justified in these patients concomitant coronary artery disease had to be excluded on clinical grounds alone. Thus the patients in this study had arterial hypertension without clinically evident coronary artery disease.

The patients consented to the following tests, which were performed before introduction of antihypertensive treatment or four weeks after its discontinuation. Eight (42%) patients in group 1, 11 (44%) patients in group 2A, and five (38%) patients in group 2B had been treated with antihypertensive agents more than four weeks before the study. The duration of treatment was 4·8 (1·5) years in group 1, 3·7 (2·7) years in group 2A, and 4·4 (3·3) years in group 2B. In group 1 five (33%) patients had been on a thiazide, five (33%) on β blockers, three (17%) on methyldopa, two (11%) on calcium antagonists, and one (6%) on hydralazine; in group 2A eight (38%), seven (33%), two (10%), two (10%), one (5%) had been on the same drugs, and one (5%) had been on captopril; and in group 2B the corresponding figures were three (38%), three (38%), one (13%), and α blocker in one (13%). Thus there were no significant differences in the treatment before the tests among the groups.

ESTIMATION OF LEFT VENTRICULAR STRUCTURE AND FUNCTION

M mode and cross sectional echocardiograms were obtained with a Toshiba SSH-11A cross sectional ultrasonoscope with a 2·25 MHz transducer. A cross sectional echocardiogram was recorded on a video system (Victor Umatic CR 6060) and M mode echocardiograms were photographed on light sensitive paper (Kodak Linagraph, 1985) at a paper speed of 50 mm/s using a Honeywell 1956 strip chart recorder. The echocardiograms were obtained during expiration. The measurements were performed by two observers (who were unaware of the patient's clinical state) from at least six consecutive cardiac cycles. The thickness of the interventricular septum and ventricular posterior wall was measured at the time of the R wave on the electrocardiogram (end diastole), with the ultrasonic beam directed just below the tip of the anterior mitral leaflet on M mode echocardiograms. The left ventricular diameter was measured as the distance between the echoes of the left ventricular posterior wall and of the interventricular septum, just below the tip of the mitral leaflets at the level of the chordae tendineae. The diameter of the left ventricle was measured at end diastole and end systole (when the endocardial surface of septum was closest to the posterior wall of the left ventricle). All measurements were made with a centimetre scale superimposed on the echocardiogram. Fractional shortening (an index of the ejection phase) was calculated as left ventricular end diastolic diameter minus left ventricular end systolic diameter divided by left ventricular end diastolic diameter, and the result was expressed as a percentage.

Left ventricular mass was calculated by a pathologically validated regression method: 1·04 (left ventricular end diastolic diameter + interventricular septal and posterior wall thicknesses)^3—left ventricular end diastolic diameter^3) − 14.[3]

The end systolic wall stress was calculated by the equation: (peak arterial pressure) × (left ventricular end systolic diameter)^2/4 (left ventricular wall thickness) × (left ventricular end systolic diameter + wall thickness).[4] This is an expression of the average meridional wall stress which may be defined as the force per unit area acting at the equatorial plane of the ventricle in the direction of the apex-to-base axis. The calculation of end systolic wall stress from these measures has been validated.[5,6]

Table 1 shows the normal values of haemodynamic variables obtained from 22 healthy subjects in our

Table 1 *Data (mean (SD)) used to calculate left ventricular mass and end systolic stress in 22 healthy volunteers (mean (SD) age 46 (10) years, 17 men and 5 women) in whom physical and laboratory examinations did not show any abnormality*

Variable	*Value*
Heart rate (beats/min)	70 (8)
Systolic blood pressure (mm Hg)	127 (13)
Diastolic blood pressure (mm Hg)	80 (9)
Left ventricular end diastolic diameter (mm)	48 (3)
Left ventricular end systolic diameter (mm)	30 (3)
Fractional shortening (%)	37 (5)
Interventricular septal wall thickness (mm)	9 (1)
Left ventricular posterior wall thickness (mm)	10 (1)
Left ventricular mass (g)	180 (30)
Left ventricular end systolic stress (g/cm^2)	60·8 (12·2)
Plasma noradrenaline (pg/ml)	148 (41)

laboratory. These are not significantly different from those of other investigators.[3 4]

The patients were separated into two groups: group 1 consisted of 19 patients with end systolic wall stress < 2 SD below the normal mean ($< 36\cdot4$ g/cm^2) and group 2 consisted of 38 patients with end systolic wall stress within 2 SD of the normal mean. (No patient in this study had end systolic wall stress more than 2 SD above the normal mean.) It has been reported that the mean left ventricular mass calculated echocardiographically in hypertensive patients with left ventricular hypertrophy is approximately twice the normal mean value.[7 8] So we divided group 2 into two subgroups: group 2A consisted of 25 patients with calculated left ventricular mass of twice the normal mean or smaller ($\leqslant 360$ g) and group 2B consisted of 13 patients with left ventricular mass more than twice the normal mean (> 360 g).

We studied the effect of isoproterenol by comparing the relation between fractional shortening and end systolic wall stress before and after isoproterenol. End systolic wall stress was reduced by isoproterenol. To increase the accuracy of the regression line of the relation between fractional shortening and end systolic wall stress before isoproterenol we increased the number of measurements for smaller end systolic wall stress before isoproterenol in 10 patients (five of group 1, four of group 2A, and one of group 2B) by slow infusion of a solution of sodium nitroprusside (25 mg/500 ml). Left ventricular dimension and arterial pressure were recorded every 30 s during the infusion, until the peak arterial pressure decreased by 30% of the initial value or the heart rate increased by 10% of the initial value, because chronotropic change may influence the inotropic effect.[4]

ADRENERGIC RESPONSES

Plasma noradrenaline

Before the start of echocardiographic examination after isoproterenol infusion we collected venous blood samples to determine plasma noradrenaline. Samples were collected after the subject had rested supine for at least 20 minutes with an indwelling butterfly needle in an arm vein. Plasma was separated in a refrigerated centrifuge at 2°C and stored at −40°C. Noradrenaline was adsorbed on to activated alumina at pH 8·55 by adding Tris-HCl buffer (pH 8·55). Noradrenaline-adsorbed alumina was washed by water followed by elution with 100 μl of 0·25 mol/l acetic acid. After purification with alumina, noradrenaline was separated by high-performance liquid chromatography and was measured spectrofluorometrically by the trihydroxyindole method (Shimadzu spectrofluorometer RF-500 LCA). (Table 1 shows the normal value.)

Isoproterenol echocardiography

The study was performed in the afternoon in all patients. Simultaneous cross sectional and M mode echocardiographic and electrocardiographic baseline recordings and blood pressure measurements were performed with the patient in a supine position immediately before intravenous infusion of isoproterenol (0·02 μg/kg/min) via a calibrated infusion pump. After 5 minutes' infusion, cross sectional and M mode echocardiograms and an electrocardiogram were recorded and blood pressure was measured by cuff sphygmomanometer. The transducer was held at the same part on the chest wall throughout the examinations. To standardise the technique between patients, as well as in the same patient before and after the infusion of isoproterenol, we tried to record the echocardiograms at the same part of the left ventricle (just below the tip of the anterior mitral leaflet) before and after the infusion of isoproterenol. The beams of M mode echocardiography were aligned perpendicularly with the posterior walls of the left ventricle and with the wall of the interventricular septum in all the patients both before and after the infusion of isoproterenol.

STATISTICAL ANALYSIS

We used the *t* test, paired *t* test, correlation, regression equations, F test, and one-way analysis of variance as appropriate. All results in which $p < 0\cdot05$ were regarded as statistically significant.

Results

HAEMODYNAMIC AND ECHOCARDIOGRAPHIC FINDINGS

Table 2 shows the values of haemodynamic, echocardiographic, and other variables before the infusion of isoproterenol. There were no significant differences in age, sex, and heart rate among the groups. Systolic blood pressure was significantly lower in group 1 than in groups 2A and 2B ($p < 0\cdot01$ and $p < 0\cdot001$ respectively). Left ventricular end diastolic and end systolic diameters were significantly smaller in group 1 than in groups 2A and 2B ($p < 0\cdot05$ and $p < 0\cdot05$; $p < 0\cdot001$ and $p < 0\cdot001$ respectively). Fractional shortening was significantly larger in group 1 than in groups 2A and 2B ($p < 0\cdot001$ and $p < 0\cdot001$ respectively), but there was no significant difference between group 2A and group 2B. The interventricular septum was significantly thicker in groups 1 and 2B than in group 2A ($p < 0\cdot001$), but there was no significant difference in the thickness of the posterior wall among the groups. There was asymmetric septal hypertrophy (interventricular septal thickness: posterior wall thickness $\geqslant 1\cdot3$) in seven (37%) patients in group 1, 2 (8%) patients in group 2A, and five (38%)

Table 2 *Results (mean (2 SD)) of the study population at baseline*

Variables	*Group* 1	2A	2B	*p values* 1 vs 2A	2A vs 2B	1 vs 2B
No	19	25	13			
Age (years)	51/7	47/7	50/11	NS	NS	NS
Men/women	16/3	19/6	11/1	NS	NS	NS
Heart rate (beats/min)	65 (10)	69 (11)	66 (11)	NS	NS	NS
Systolic blood pressure (mm Hg)	151 (13)	168 (19)	172 (15)	<0 01	NS	<0 001
Diastolic blood pressure (mm Hg)	101 (9)	109 (12)	106 (14)	<0 05	NS	NS
Left ventricular end diastolic diameter (mm)	44 (4)	47 (4)	47 (3)	<0 05	NS	<0 05
Left ventricular end systolic diameter (mm)	21 (3)	29 (4)	31 (4)	<0 001	NS	<0 001
Fractional shortening (%)	52 (4)	39 (7)	34 (7)	<0 001	NS	<0 001
Interventricular septal thickness (mm)	17 (3)	14 (2)	18 (2)	<0 001	<0 001	NS
Left ventricular posterior wall thickness (mm)	14 (2)	14 (2)	15 (2)	NS	NS	NS
Left ventricular mass (g)	339 (62)	307 (39)	404 (45)	<0 05	—	<0 01
Left ventricular end systolic wall stress (g/cm²)	25 6 (8 5)	53 6 (12 4)	55 1 (12·7)	—	NS	—
Plasma noradrenaline (pg/ml)	140 (84)	159 (75)	302 (147)	NS	<0·001	<0 001

patients in group 2B. There was also hypertrophy in the apical region of the left ventricle in four patients in group 1 and two in group 2B. No patient had systolic anterior motion of the mitral valve. Left ventricular mass was significantly larger in group 1 than in group 2A ($p < 0{\cdot}05$) and was significantly larger in group 2B than in group 1 ($p < 0{\cdot}01$). There was no significant difference in end systolic wall stress between groups 2A and 2B.

During the infusion of sodium nitroprusside, two to five measurements were obtained in each patient before the end point—that is when the peak arterial pressure had decreased by 30% of the initial value or the heart rate had increased by 10% of the initial value. At the end point, end systolic wall stress had fallen from 39·3 (11·9) to 27·8 (10 0) g/cm² with an increase of fractional shortening from 46 (5) to 49(5).

Figure 1 shows the relation between fractional shortening and end systolic wall stress for 57 measurements obtained before the infusion of isoproterenol in all the patients and 35 measurements obtained during the infusion of sodium nitroprusside. There was a statistically significant inverse linear relation between fractional shortening and end systolic wall stress (slope $-0{\cdot}448$, $r = 0{\cdot}879$, $p < 001$, $\alpha < 0{\cdot}005$) when the end systolic wall stress was 12 g/cm².

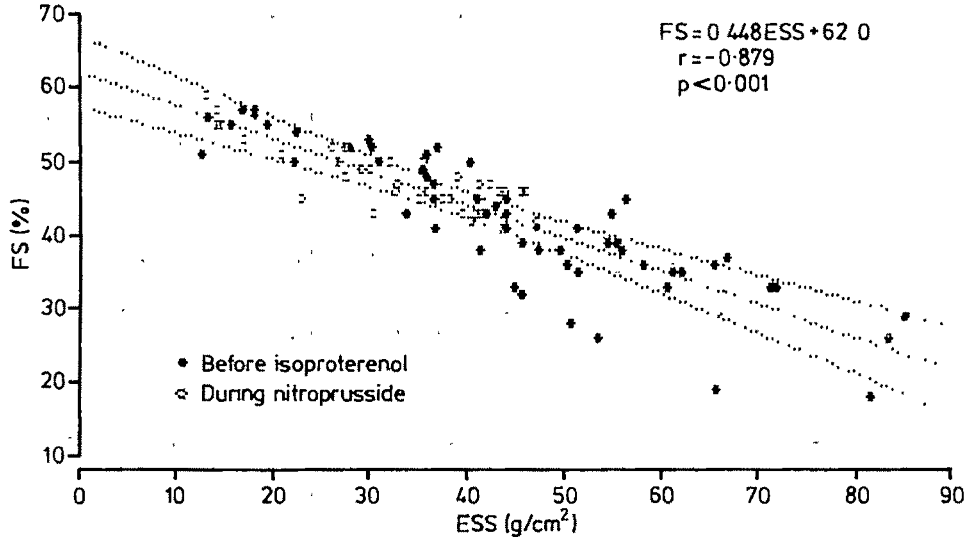

Fig 1 *Relation between left ventricular end systolic wall stress (ESS) and fractional shortening (FS) before and during the infusion of isoproterenol. There was a significantly negative linear relation when ESS was > 12 g/cm². The broken lines show the regression line and the confidence interval.*

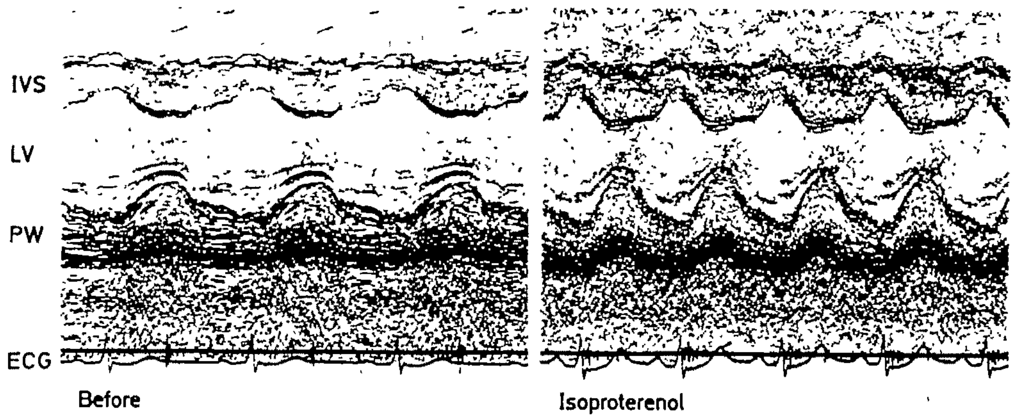

Fig 2 *Echocardiograms before and after the infusion of isoproterenol in a 47 year old man. IVS, interventricular septum, LV; left ventricular cavity; PW, left ventricular posterior wall.*

ADRENERGIC RESPONSES

Plasma noradrenaline

The concentration of plasma noradrenaline was significantly higher in group 2B than in groups 1 and 2A ($p < 0{\cdot}001$ respectively) (table 2).

Effect of isoproterenol on echocardiographic variables

Figure 2 shows echocardiograms obtained before and after the infusion of isoproterenol in a 47 year old man. The echoes of the left side of the interventricular septum and of the endocardium of the left ventricular posterior wall can be seen clearly in both of the echocardiograms. The presence of echoes from the chordae tendineae indicates that both these echocardiograms are from the same part of the left ventricle. Infusion of isoproterenol caused hyperkinesis. Clear echocardiograms were obtained from the same part of the left ventricle before and after the infusion of isoproterenol in all but five patients (one in group 1, two in group 2A, and two in group 2B). In three patients in group 1, end systolic wall stress decreased to below 12 g/m^2. These three patients were excluded from the analysis of the effect of isoproterenol because the linear relation between fractional shortening and end systolic wall stress operated only when end systolic wall stress was > 12 g/cm^2 (figure 1).

Infusion of isoproterenol increased the mean (SD) heart rate from 66 (9) to 97 (17) beats/min +32 (11) in group 1, from 70 (11) to 101 (13) +32 (8) in group 2A, and from 65 (11) to 96 (19) +31 (12) in group 2B. There were no significant differences among the groups. Systolic blood pressure changed (but not significantly) from 151 (9) to 160 (15) mm Hg in group 1, from 169 (19) to 180 (22) mm Hg in group 2A, and from 171 (15) to 165 (28) mm Hg in group 2B. Diastolic blood pressure decreased from 100 (9) to 90 (14) mm Hg in group 1, from 110 (12) to 95 (13) mm Hg in group 2A, and from 103 (13) to 83 (14) mm Hg in group 2B ($p < 0{\cdot}001$ in each group). Left ventricular end diastolic diameter did not change significantly (44 (4) to 44 (3) mm in group 1, 47 (4) to 46 (4) mm in group 2A, and 47 (4) to 46 (4) mm in group 2B). Left ventricular end systolic diameter decreased from 21 (3) to 17 (2) mm in group 1, from 29 (4) to 23 (4) mm in group 2A, and from 31 (3) to 25 (4) mm in group 2B ($p < 0{\cdot}001$ in each group).

Fractional shortening increased from 52 (4) to 62 (4)% in group 1, from 39 (7) to 50 (9)% in group 2A, and from 34 (6) to 45 (6)% in group 2B ($p < 0{\cdot}001$ in each group). End systolic wall stress decreased from 26·2 (7·6) to 17·2 (5·5) g/cm^2 in group 1, from 53·3 (12 1) to 37·3 (14·1) g/cm^2 in group 2A, and from 53·0 (10·6) to 33·0 (10·4) g/cm^2 in group 2B. Figure 3 shows the changes of the relation between fractional shortening and end systolic wall stress in each group. It suggests that there was a different slope for each of the groups. Figure 4 shows the increase of fractional shortening corrected for the decrease of end systolic wall stress, that is the slope of the change of the relation between fractional shortening and end systolic wall stress. This variable (Δ fractional shortening $/ - \Delta$ end systolic wall stress) shows the response of myocardial contractility to isoproterenol because the changes in this variable are within the range in which fractional shortening and end systolic wall stress are linearly related in fig 1. The increase in fractional shortening was significantly larger in group 1 (1·40 (0·60) cm^2/g) than in group 2A (0·85 (0·39) cm^2/g) ($p < 0$ 05) and was significantly larger in group 2A than in group 2B (0·56 (0 15) cm^2/g) ($p < 0{\cdot}05$).

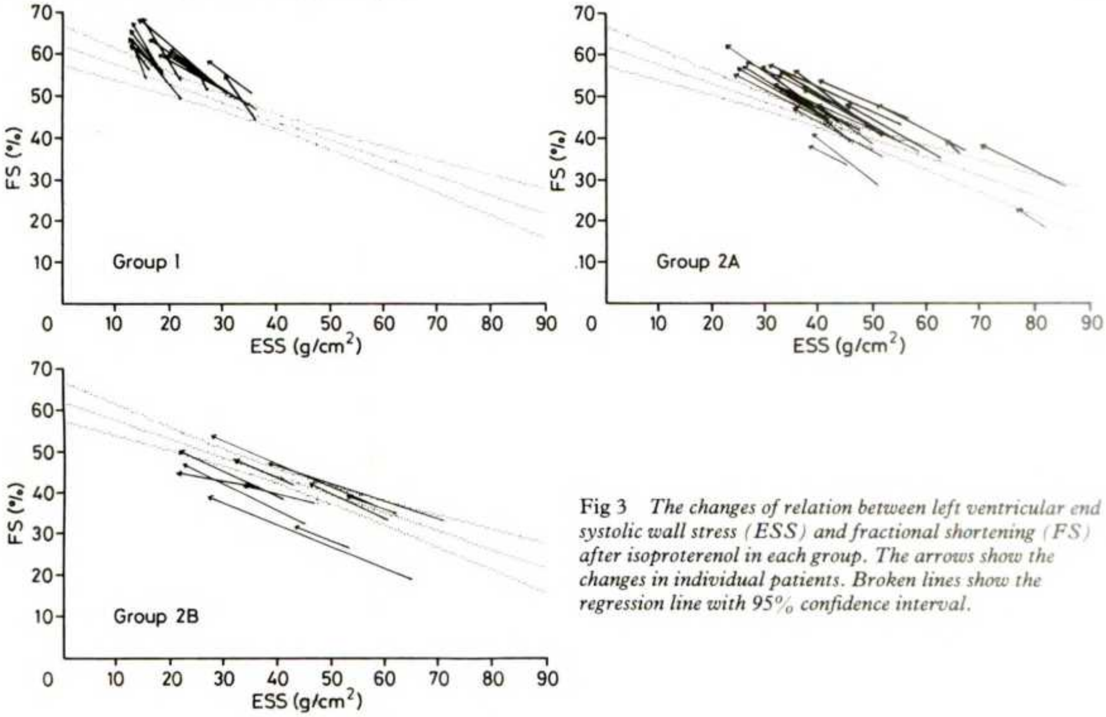

Fig 3 *The changes of relation between left ventricular end systolic wall stress (ESS) and fractional shortening (FS) after isoproterenol in each group. The arrows show the changes in individual patients. Broken lines show the regression line with 95% confidence interval.*

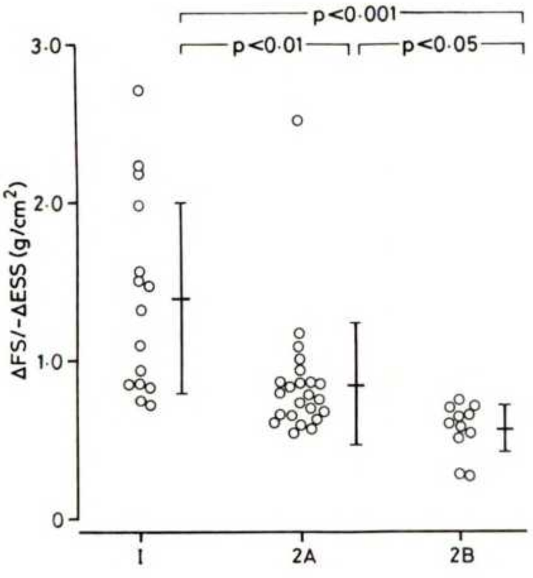

Fig 4 *The increase of fractional shortening produced by infusion of isoproterenol (ΔFS) after correction for the decrease of left ventricular end systolic wall stress (ΔESS) (ΔFS/−ΔESS).*

Discussion

ECHOCARDIOGRAPHIC STUDY OF MYOCARDIAL MECHANICS

Echocardiographic measurements of left ventricular dimensions are known to be reliable.[9 10] Changes of less than 2 mm in the echocardiogram do not represent clinically significant changes. In the present study, we used the echocardiographic method to calculate left ventricular mass and wall stress, as have others.[4 9] Even small measurement errors in wall thickness may significantly influence left ventricular mass and wall stress; however, the values we obtained in the present study resembled those obtained by others.[4 9] The reported relative errors of fractional shortening and end systolic wall stress are about 0·4% and 25% respectively.[11] So the differences in △ fractional shortening /− △ end systolic wall stress that we found among our study groups are likely to be real because they were all more than 26%.

CARDIAC HYPERTROPHY

Chronic pressure overloading of the heart is believed to lead to wall thickening that is commensurate with the increased systolic pressure and tends to normalise myocardial wall stress[12,13] (appropriate hypertrophy). In hypertrophic cardiomyopathy, however, there is inappropriate hypertrophy in response to pressure overload.[14] Such hypertrophy must be caused by factors other than mechanical overload.

LEFT VENTRICULAR EJECTION PHASE INDICES AND WALL STRESS

An immense linear correlation was found between fractional shortening and ejection fraction and left ventricular wall stress in normal controls,[15] in hypertension,[9] and in other heart diseases.[16,17] An inverse curvilinear correlation has also been reported between the velocity of left ventricular fibre shortening and left ventricular wall stress.[16] In our study we used Δfractional shortening $/-\Delta$end systolic wall stress as an index of the response of myocardial contractility in the range in which fractional shortening and end systolic wall stress were considered to be related linearly in fig 1.

To exclude the possibility that Δfractional shortening $/-\Delta$end systolic wall stress might have been larger in the cases with a smaller end systolic wall stress, we performed isoproterenol echocardiography in three patients who had left ventricular hypertrophy but no aortic pressure gradient because they had had a valve replacement for aortic stenosis (table 3). They had small end systolic wall stress with a small value for Δfractional shortening $/-\Delta$end systolic wall stress. This indicates that Δfractional shortening $/-\Delta$end systolic wall stress is a valid index of the response of myocardial contractility; the number of the cases is small, however.

The relation between indices of left ventricular ejection and afterload may also be influenced by a change of preload; however, this effect can be ignored in this study because the left ventricular end diastolic diameter did not change with isoproterenol infusion in any of the groups.

Table 3 *Results (mean (SD)) of isoproterenol echocardiography in three patients with left ventricular hypertrophy who had had valve replacement for aortic stenosis and had no aortic pressure gradient*

Variable	*Baseline*	*Isoproterenol*
Age (yr)	56 (2)	
Sex (M/F)	2:1	
Heart rate	68 (14)	105 (33)
Systolic blood pressure (mm Hg)	128 (19)	119 (17)
Diastolic blood pressure (mm Hg)	75 (10)	63 (17)
Left ventricular end diastolic diameter (mm)	41 (1)	40 (2)
Left ventricular end systolic diameter (mm)	23 (4)	21 (4)
Fractional shortening (%)	43 (8)	47 (7)
Interventricular septal wall thickness (mm)	17 (2)	
Left ventricular posterior wall thickness (mm)	18 (1)	
Left ventricular mass (g)	381 (71)	
Left ventricular end systolic stress (g/cm^2)	26·7 (9·1)	20·8 (7·6)
Δfractional shortening$/-\Delta$end systolic wall stress (cm^2/g)		0·57 (0·25)

ADRENERGIC RESPONSE IN HYPERTENSIVE HYPERTROPHY

It has been suggested that, as well as mechanical factors, neurohormonal influences could have an important role in the cardiac hypertrophy of hypertension.[18] Small doses of isoproterenol or other catecholamines produced hypertrophy in laboratory animals without changing blood pressure and heart rate.[19,20]

The aetiology of hypertrophic cardiomyopathy is not yet known. A disorder of catecholamine function has been suggested,[21] and hypersensitivity of the β adrenergic receptor system has been proposed to explain hypertrophic cardiomyopathy with asymmetric septal hypertrophy.[22]

Whether the presence of asymmetric septal hypertrophy in hypertensive patients is the result of a strong response to an increased afterload or is a coincidental occurrence is not clear. In our study, asymmetric septal hypertrophy was more common in groups 1 and 2B than in group 2A. It may be that the mechanisms of asymmetric septal hypertrophy differed in groups 1 and 2B. The adrenergic response in group 1 resembled that found in hypertrophic cardiomyopathy, whereas that in group 2B resembled the response to high arterial pressure.

In patients in group 1 end systolic wall stress was less than normal, and these patients were more responsive to isoproterenol than those with the other types of hypertensive hypertrophy. Hypertrophy in group 1 may be the result of a combination of the hypertension and a factor causing hypertrophic cardiomyopathy; this second factor will be difficult to identify since in hypertrophic cardiomyopathy, by definition, there is no cause established. Alternatively, patients in group 1 may have had an early stage of hypertension; this is not likely, however, as these patients were not young and they had had hypertension for at least five years.

Group 2B (severe hypertrophy) was significantly less responsive to isoproterenol than group 2A (mild hypertrophy) ($p < 0·01$). This clinical result may support the experimental results of others.[23] The blunting of inotropic responsiveness to β adrenergic stimulation may be one of the mechanisms causing progression from left ventricular hypertrophy to heart failure in hypertensive disease.

The degree of left ventricular hypertrophy has been reported to be positively related to circulating concentrations of plasma noradrenaline.[24] But this relation is still controversial. In our study, increased concentrations of plasma noradrenaline were found only in group 2B. Patients in group 1 had normal plasma noradrenaline. Perhaps the increase in plasma noradrenaline in hypertensive hypertrophy is a secondary phenomenon. A depressed β adrenergic reserve might prompt a compensatory increase in plasma noradrenaline.

CLINICAL IMPLICATIONS

Our study showed that inotropic responsiveness to isoproterenol infusion was higher in hearts with lower than normal values for end systolic wall stress than hearts with other types of hypertensive hypertrophy, although hypertrophy in the former group was not mild. On the other hand, patients with normal end systolic wall stress and severe hypertrophy were less responsive to β adrenergic stimulation than those with the other hypertensive hypertrophy. The inotropic responsiveness to isoproterenol might be regulated by the conditions of β adrenergic receptors in the myocardium when myocardial contractility is normal. Myocardial contractility did not appear to differ among the three groups—groups 1 and 2 seemed to be on the same regression line in fig 1. Groups 2A and 2B did not show significantly different fractional shortening and end systolic wall stress.

In hypertensive patients with subnormal end systolic wall stress and increased responsiveness to isoproterenol, cardiac hypertrophy (inappropriate hypertrophy) may have been induced by a non-mechanical (probably neurohormonal) factor; but in those with normal end systolic wall stress the cardiac hypertrophy (appropriate hypertrophy) might have been induced by a mechanical factor (for example high arterial pressure) and might progress to left ventricular dysfunction with impairment of β adrenergic reserve and increased plasma noradrenaline. Thus classification of hypertensive hypertrophy according to the contribution made by a mechanical factor (left ventricular systolic wall stress) and a non-mechanical factor (β adrenergic response) may be useful in identifying the aetiology and pathophysiology in individual patients.

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Case reports

Percutaneous coronary angioplasty in a cardiac transplant recipient

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*From the Department of Cardiovascular Medicine, University of Birmingham, East Birmingham and Queen Elizabeth Hospitals, Birmingham and *British Heart Foundation Heart Transplant Research Unit, Papworth Hospital, Cambridge*

SUMMARY Two years after an orthotopic cardiac transplant a 28 year old man was found to have clinically significant stenosis of the right coronary artery at routine coronary angiography. This lesion was accompanied by a perfusion defect on exercise thallium scintigraphy.

Percutaneous transluminal coronary angioplasty of the lesion improved the angiographic appearance of the stenosis and reduced the exercise thallium perfusion defect.

The development of coronary artery disease in the transplanted heart is a cause for concern as it is usually asymptomatic and may progress rapidly,[1] leading to silent myocardial infarction, cardiac failure, or sudden death.[2] Retransplantation has been performed in cases in which coronary atherosclerosis had progressed to diffuse, extensive involvement of epicardial vessels.[1 3] Early detection of coronary disease is therefore important and most centres practise annual angiography of the coronary vessels, usually after the first two years. Because the transplanted heart is denervated, anginal symptoms are absent even when there is severe disease. The most useful approach to management of early discrete lesions is uncertain.

We report a case in which a significant discrete stenosis of the right coronary artery was discovered two years after transplantation; this was treated by percutaneous transluminal coronary angioplasty with a good result.

Case report

A 26 year old man underwent orthotopic cardiac transplantation in November 1984 because of intractable congestive cardiac failure after a large anterior wall myocardial infarction caused by occlusion of the left anterior descending coronary artery. The other two vessels were normal. He was a non-smoker with a normal lipid profile, but he had a strong family history of coronary artery disease. The donor heart came from a 43 year old man with no history suggestive of coronary artery disease. There was also no evidence of coronary artery disease when the donor heart was inspected at the time of its removal. After transplantation, cyclosporin B and azathioprine were given for immunosuppression and aspirin and dipyridamole were also given. The postoperative course was complicated only by a persistent nodal rhythm resulting in bradycardia (45–50 beats/min); this was, however, asymptomatic. A permanent, epicardial pacemaker (Medtronic Spectrax, VVI) had been fitted as a standard procedure at the time of transplant, and the device produced occasional episodes of ventricular paced rhythm. He was discharged home on the 35th postoperative day and returned to a normal active life. He experienced no clinical or histological rejection episodes in the next two years but at routine coronary angiography in November 1986 he was found to have an appreciable stenosis of the mid-right coronary artery (fig 1a). Exercise thallium scintigraphy showed a large defect in the lateral segment with moderate reperfusion in the resting images at four hours after exercise (fig 2a).

In view of these abnormalities, percutaneous transluminal coronary angioplasty of the right coronary artery was undertaken in February 1987. A femoral approach was used with the standard technique of dilatation with a steerable 3·0 mm balloon catheter and a Judkins' guiding catheter. There was no residual angiographic stenosis or complications after dilatation of the lesion (fig 1b). Repeat exercise thallium scintigraphy at six weeks after angioplasty showed a smaller lateral perfusion defect than demonstrated before, but there was no evidence of reperfusion at four hours after exercise (fig 2b). The

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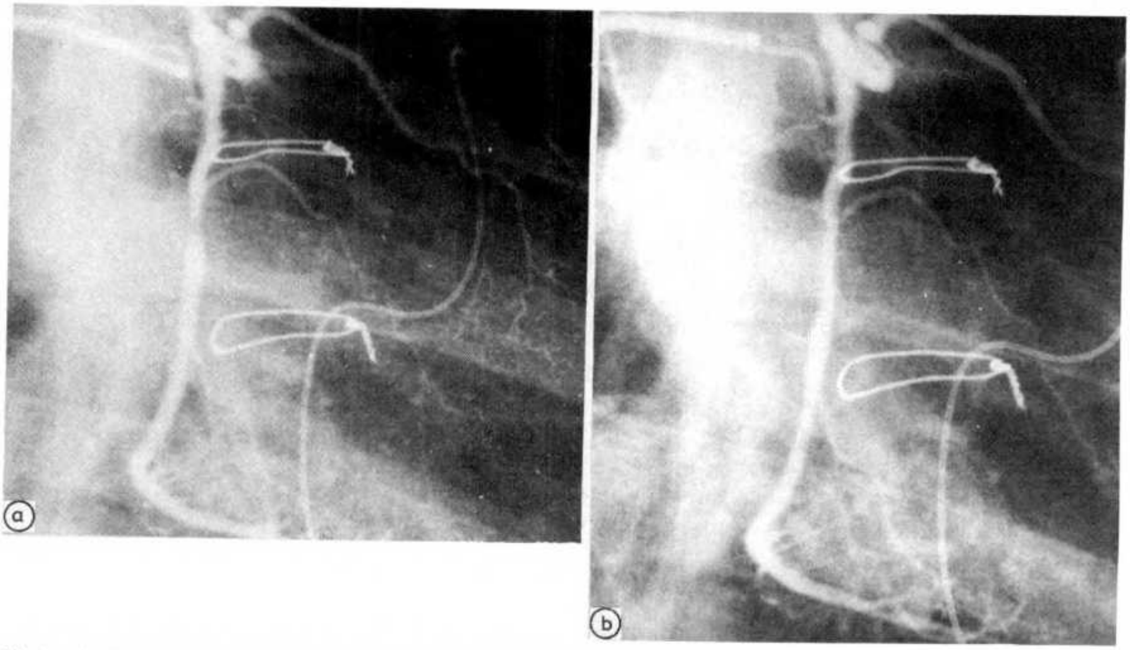

Fig 1 *Angiogram of the right coronary artery (right anterior oblique view) showing (a) significant stenosis in the mid-section and (b) the same view after angioplasty.*

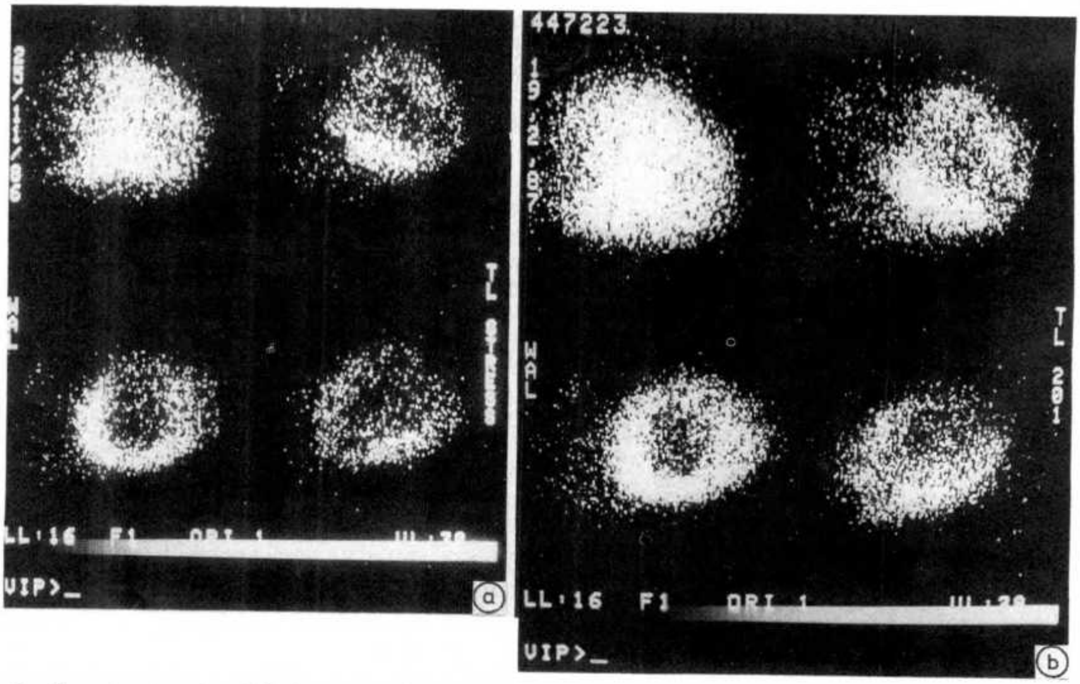

Fig 2 *Four-view (anterior, 30° left anterior oblique, 60° left anterior oblique, left lateral) thallium-201 scintigram (stress images) showing (a) large defect in the lateral segment (top right) before angioplasty and the same views (b) six weeks after angioplasty showing some improvement in perfusion.*

patient remains well and continues to have a good exercise tolerance. Repeat coronary angiography at six months after angioplasty showed a patent right coronary artery with good remodelling and only minor residual stenosis.

Discussion

The aetiology of accelerated coronary occlusive disease in some transplanted hearts is imperfectly understood. It is likely that rejection is a feature, at least as an initiating factor, and both cytotoxic B-cell antibodies and hypercholesterolaemia have been implicated in the pathogenesis.[4] Our own experience indicates that there is angiographic evidence of disease in 25% of patients five years after transplantation, whereas others have reported an incidence of 40% at five years.[1] Whatever the true figure, coronary artery disease is undoubtedly the most important determinant of survival in the medium and long term after transplantation and if it is severe retransplantation may be required.

There are two reports of angioplasty in transplanted hearts in the United States.[5 6] In both there was multivessel rather than single vessel disease. Our patient had an isolated lesion and, as the donor was a 43 year old man, it is possible that this was present in the donor organ at the time of transplantation. This cannot be disproved because the first angiogram was performed at two years. Initially it was our practice to perform angiography once a year from the first year onwards, but we no longer do this because the incidence of disease at one year was so low. Nevertheless, the lesion may have developed between transplantation and the angiogram at two years as, although accelerated coronary occlusive disease is often diffuse, we have found the appearance of segmental lesions after previously normal angiograms within this period.

The role of myocardial perfusion imaging with thallium-201 in the transplanted heart is less well defined than its role in "native" coronary artery disease.[7] The single reported case presenting scintigraphic data[6] demonstrated an improvement of regional perfusion in the area of a previous perfusion defect after angioplasty of the stenosed vessel supplying the region, but other studies of thallium-201 imaging in the transplanted heart with diffuse small vessel disease have demonstrated a poor sensitivity in these circumstances.[1]

Angioplasty has now been shown to be technically possible in the transplanted heart with single or multiple vessel disease; the long term results in terms of patient and graft survival or vessel patency remain to be assessed.

We wish to thank Professor WA Littler for permission to report the case of a patient under his care. We also thank Dr Hywel Davies for his invaluable assistance in the preparation of this report.

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Br Heart J 1988;**59**:256–8

Possible role of coronary spasm in acute myocardial infarction precipitated by hyperventilation

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SUMMARY Acute myocardial infarction was precipitated by hyperventilation in a 65 year old man. His coronary arteriogram in the chronic phase showed almost normal coronary arteries. Injection of acetylcholine (50 μg) into the left coronary artery induced spasm of the circumflex artery with chest pain in association with ST-segment elevation in the inferior leads and ST-segment depression in the precordial leads.

In this patient there may have been atherosclerosis of the coronary arteries with absent or dysfunctional endothelium, despite an almost normal angiographic appearance. In the absence of endothelium the response of the smooth muscle to acetylcholine is constriction.

Knowledge of the pathogenesis of acute myocardial infarction is still incomplete, but there is some evidence that coronary spasm has a role.[1-3]

We report a patient in whom an acute myocardial infarction was precipitated by hyperventilation and in whom intracoronary injection of acetylcholine induced coronary spasm in the chronic phase.

Case report

A 65 year old man was admitted to our hospital because he had a syncopal attack. He had been well and had had no chest pain until three months before, when he had a syncopal attack lasting a few minutes after an operation on his hand. He had appreciable bradycardia but no chest pain at the time.

On admission the electrocardiogram showed sinus bradycardia but no ST-segment changes. He was asked to hyperventilate for an electroencephalographic test to investigate the syncopal attack. A few minutes after hyperventilating he felt chest discomfort which developed into chest oppression lasting more than an hour. The electrocardiogram taken at that time showed considerable ST-segment depression in leads II, III, aVF, and V2–V6 and an increase in serum creatine kinase to 356 IU (normal range 32–166 IU for men in our laboratory). Non-transmural myocardial infarction was diagnosed. A month later

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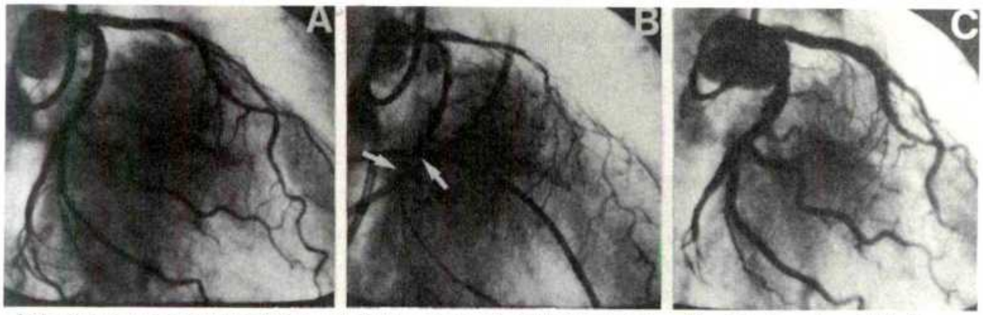

Fig 1 *Left coronary arteriograms before and during an attack of chest pain induced by injection of acetylcholine (50 µg) into the left coronary artery and after the administration of glyceryl trinitrate. (a) Left coronary arteriogram before injection of acetylcholine. (b) Two minutes after injection of acetylcholine the obtuse marginal branch and posterior descending artery (white arrows) were occluded and were not visualised. (c) After administration of glyceryl trinitrate the coronary artery was considerably dilated and almost normal.*

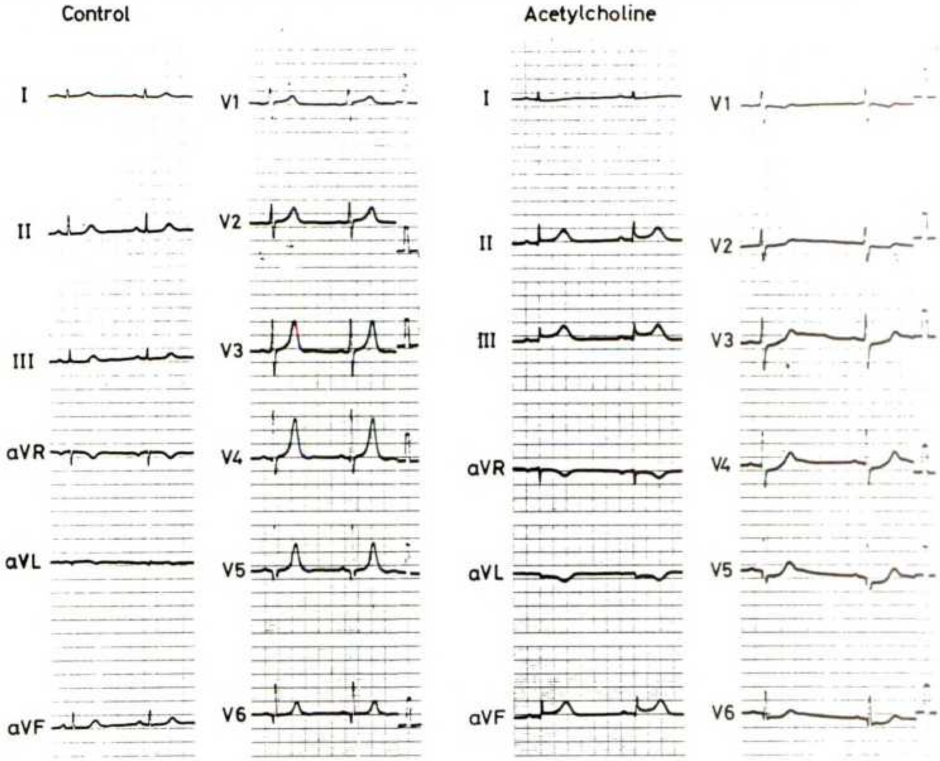

Fig 2 *(a) Electrocardiogram before intracoronary injection of acetylcholine shows sinus bradycardia but no ST-segment changes. (b) Electrocardiogram after injection of acetylcholine (50 μg) into the left coronary artery shows ST-segment depression in the precordial leads and ST-segment elevation in leads II, III, and aVF.*

cardiac catheterisation was performed. Coronary angiography, measurement of coronary sinus blood flow by thermodilution, and blood sampling were performed before and after intracoronary injection of acetylcholine. Baseline aortic blood pressure, coronary sinus blood flow, the myocardial lactate extraction ratio, and coronary vascular resistance were 165/76 mm Hg, 78 ml/min, 6·6%, and 1346 mm Hg min/l respectively. Before the administration of acetylcholine coronary angiography showed normal right and left coronary arteries with a dominant left circumflex artery giving rise to the posterior descending artery (fig 1a). Two minutes after the injection of acetylcholine (50 μg) into the left coronary artery there was ST-segment elevation in leads II, III, and aVF and ST-segment depression in leads V2–V6 (fig 2) and the patient complained of chest pain. Aortic pressure fell to 109/50 mm Hg and myocardial lactate extraction fell to −69·4%. Nevertheless, coronary sinus blood flow increased to 150 ml/min and coronary vascular resistance fell to 433 mm Hg min/l. Coronary arteriograms showed occlusion of the obtuse marginal branch and posterior descending artery of the left circumflex artery and diffuse constriction of the other segments of the left coronary artery (fig 1b). The attack and spasm disappeared after intracoronary injection of glyceryl trinitrate (200 μg) which caused considerable dilatation of the coronary artery (fig 1c).

Discussion

The attack of acute myocardial infarction in this patient was precipitated by hyperventilation and, because hyperventilation can induce coronary spasm in patients with variant angina,[4] it is possible that coronary spasm precipitated acute myocardial infarction in this patient. This theory is supported by the almost normal coronary arteriogram in the chronic phase and the induction of spasm of the circumflex artery (associated with ST-segment deviations in the inferior and precordial leads) and chest pain by intracoronary injection of acetylcholine.

Thus this report shows that hyperventilation may precipitate acute myocardial infarction, possibly by inducing coronary spasm in some patients. There are also reports of death associated with hyperventilation.[5 6] This fact is clinically important because hyperventilation is routinely performed in the electroencephalographic or ventilatory tests.

Injection of acetylcholine is generally accepted as causing coronary vasodilatation, as shown by increased coronary blood flow.[7] In our patient coronary sinus blood flow increased and coronary vascular resistance decreased after injection of acetylcholine, despite the occurrence of spasm of the left coronary artery producing myocardial ischaemia (shown by ST-segment deviations in the electrocardiogram), a decreased myocardial lactate extraction ratio, and chest pain. We propose the following explanation of this paradox: myocardial ischaemia occurred in the region of the left circumflex artery only; intracoronary injection of acetylcholine induced spasm or constriction of epicardial arteries but dilated the resistance vessels and arterioles; and the flow in the area of myocardium perfused by the artery occluded by spasm may have been decreased but the flow in other parts of myocardium may have been increased, so that the total coronary flow increased.

The present study shows that acetylcholine constricts human epicardial coronary artery in vivo and may cause coronary spasm in some patients. Recently, Furchgott and Zawadzki reported that acetylcholine can reproducibly relax arterial strips in vitro if care is taken to preserve the endothelium during preparation of the strips.[8] Contraction was observed only when the endothelium was inadvertently removed, suggesting that in the absence of endothelium the direct response of the smooth muscle is contraction. A factor that initiates the relaxation of vascular smooth muscle is released by the endothelial cells when they are exposed to acetylcholine,[8-10] and endothelial injury and proliferation of smooth muscle cells are essential in the pathogenesis of atherosclerosis.[11] It is thus possible that in this patient there was atherosclerosis of the coronary arteries with absent or dysfunctional endothelium, despite an almost normal angiographic appearance. We and Ludmer *et al* reported that intracoronary injection of acetylcholine induced coronary vasoconstriction in almost all adults, probably because most of them have atherosclerosis.[12 13]

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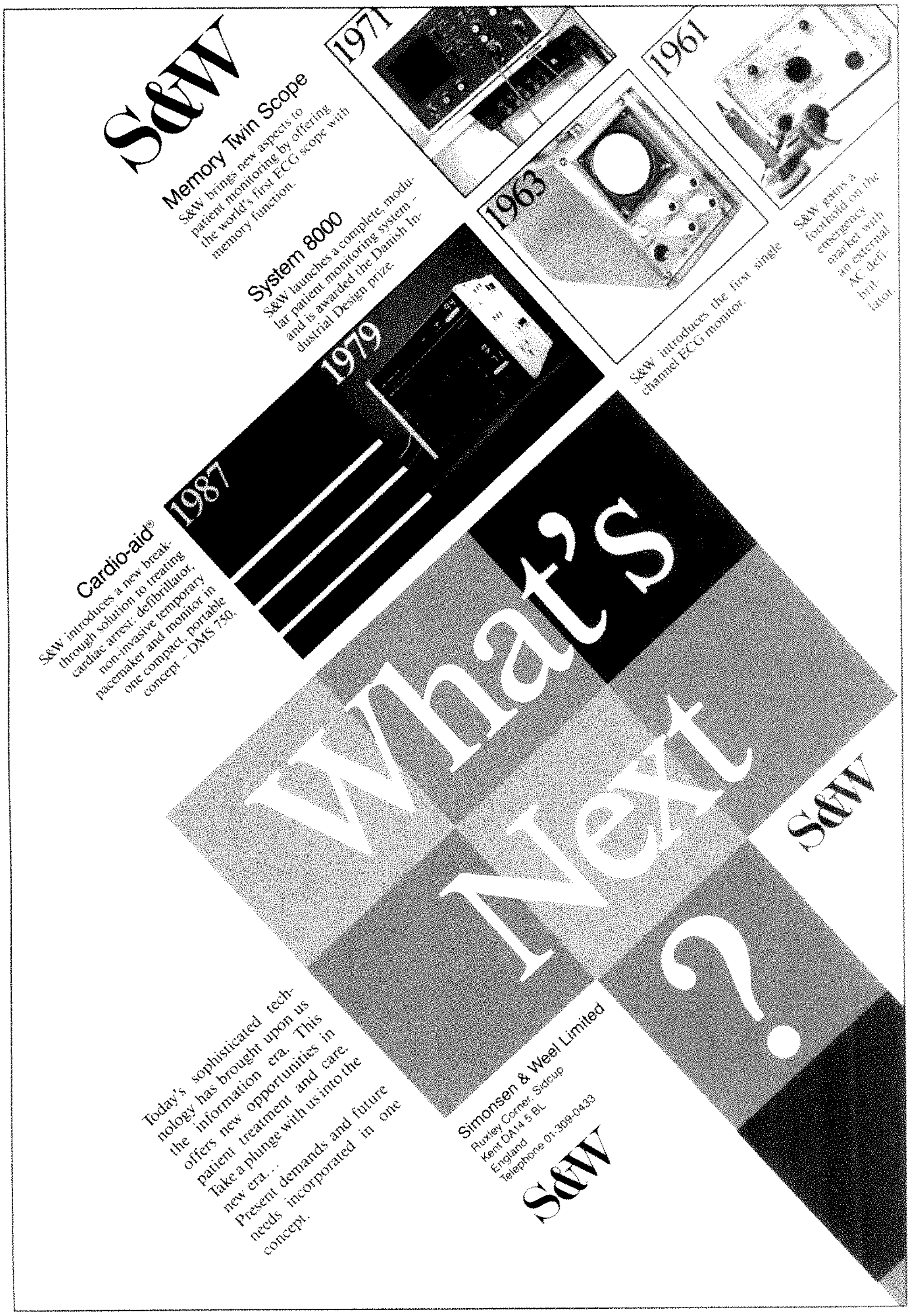

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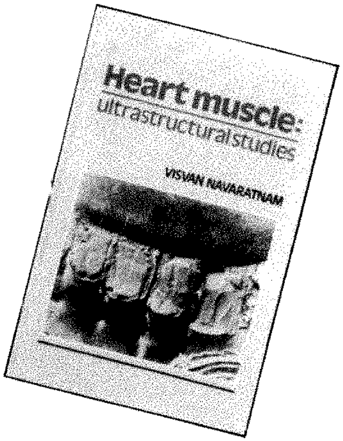

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Abolition of exercise induced ST depression after exercise training and its recurrence after β blockade

IAIN C TODD, JOHN B McGUINNESS, DAVID BALLANTYNE

From the Department of Medical Cardiology, The Victoria Infirmary, Glasgow

SUMMARY Exercise training can improve angina. A patient whose exercise tolerance test became normal after a year on an exercise programme nevertheless had a positive exercise test when he was taking a β blocker.

These results suggest that it may be undesirable to use β blockers in patients with angina who are on exercise programmes.

Case report

A 45 year old man with chronic stable angina of moderate severity for two years was enrolled in an exercise programme designed to improve his exercise tolerance. A year before he had a positive exercise test, and before he started on the exercise programme he had three more exercise tolerance tests while he was fasting. He was not on any treatment when he performed the first two tests. These two tests were identical except that on the second occasion 80 MBq of thallium was injected one minute before the end of the exercise test and a thallium myocardial perfusion scan was obtained immediately after exercise. The third test was identical with the first except that the patient had been taking 100 mg atenolol daily for one week before the test. The last dose was taken 24 hours before the exercise test.

Treatment with atenolol was started after the third test and the patient started exercise training on the Canadian Airforce 5BX plan for physical fitness.[1] In this programme the patient exercises for a maximum of 11 minutes each day at home with weekly hospital supervision. The intensity of exercise was increased each week. Within three months the patient was symptom free and within eight months he had achieved an exercise capacity in excess of that predicted for a "normal" adult of his age. The exercises were continued for a year, then the three exercise tests were repeated.

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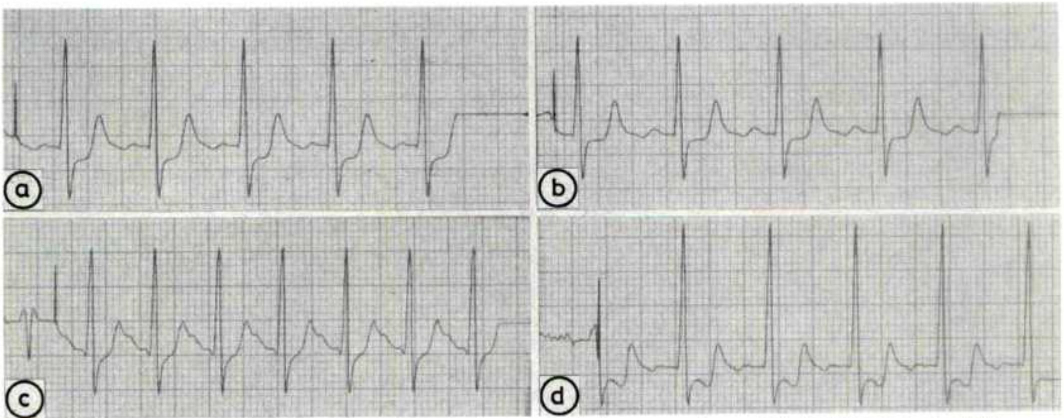

Fig 1 *Electrocardiogram of lead V_5 at the end of exercise. (a) Initial test on no drugs; (b) initial test on atenolol; (c) after training on no drugs; (d) after training on atenolol.*

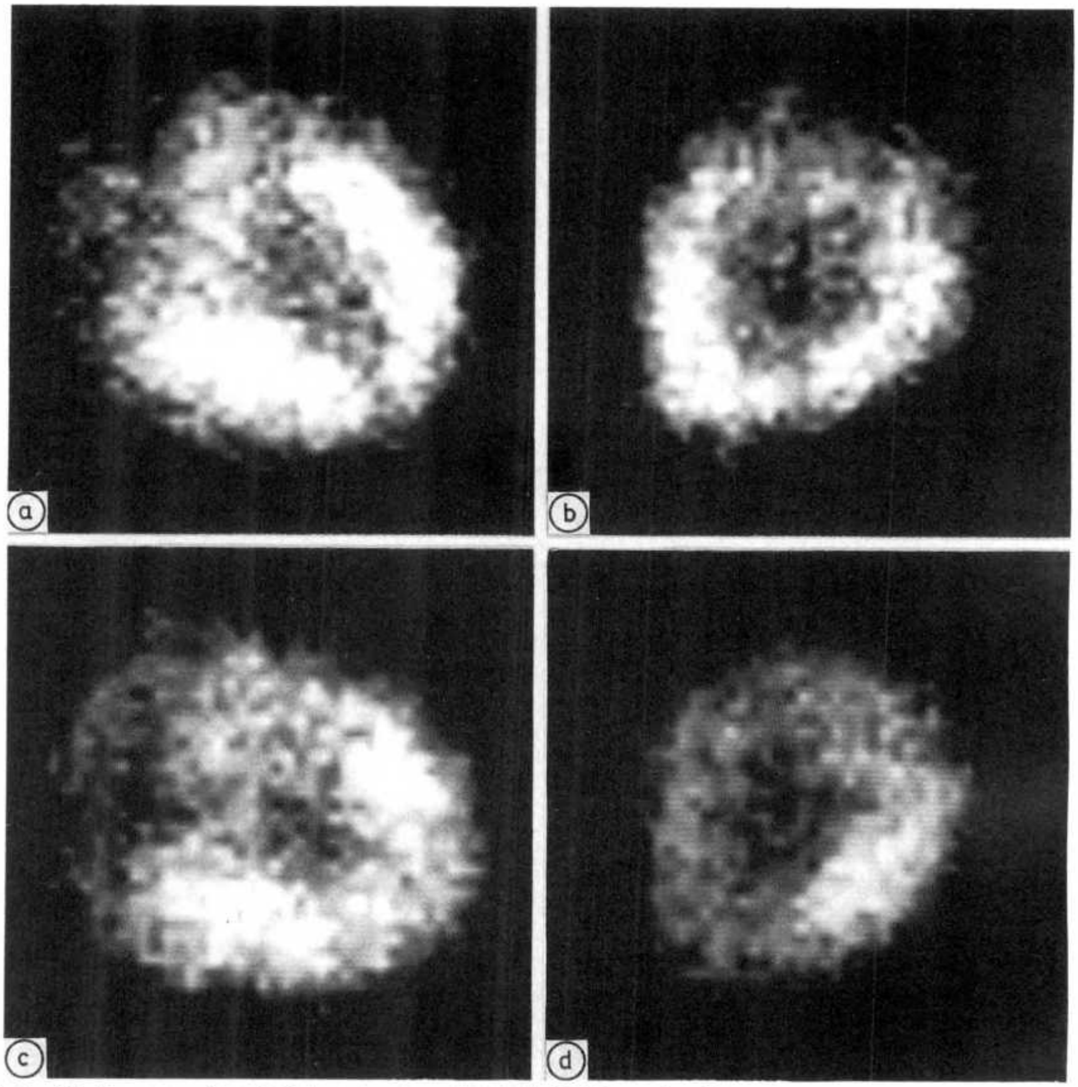

Fig 2 *Thallium scans of (a) initial anterior view; (b) initial 45° left anterior oblique view; (c) anterior view after training; (d) 45° left anterior view showing an apical defect on the initial scan with septal defect after training.*

The first two exercise tests before training had a reproducible end point. The exercise tolerance was higher on the second occasion than on the first (10 min to 3 mph and a 7·5% gradient compared with 8 min to 3 mph and a 5% gradient); this was not unexpected because the patient had become more familiar with the test. Nevertheless, the final heart rate and systolic blood pressure were identical (114 beats/min and 180 mm Hg) in the two tests. The tests were stopped because of angina. A standard 12 lead electrocardiogram showed a maximum of 2 mm ST depression in lead V4, with ST depression in V3–V5 (fig 1a). In addition, a reversible thallium defect was demonstrated in the apical region on the anterior view (fig 2a). After β blockade the patient's symptoms improved and in the third test he exercised for 23 minutes to 3 mph and a 15% gradient with a final heart rate of 101 beats per minute and systolic blood pressure of 145 mm Hg. The test ended when he became exhausted; there was ST depression of 1 mm in V4 (fig 1b).

After one year on the exercise programme the patient was able to complete all three exercise tests without symptoms. When he was not on medication he could exercise to 4·5 mph and a 25% gradient for 36 minutes. He achieved a final heart rate of 161 beats per minute and systolic blood pressure of 215 mm Hg. No ST depression was noted (fig 1c) but thallium scanning showed reversible ischaemia in the septal region on 45° left anterior oblique view (fig 2d). β blockade was again effective in reducing heart rate on exercise and the patient achieved the same end point of 36 minutes without symptoms. His final heart rate was 119 beats per minute with a systolic pressure of 190 mm Hg. Surprisingly, however, on this occasion clinically significant ST depression did occur during the test in V3–V5 with a maximum of 2 mm ST depression recorded, again in V4 (fig 1d).

In view of the considerable difference in cardiac work between the two thallium scans, a third thallium scan was obtained during an exercise test that was stopped at a double product equivalent to that during the first thallium scan. A comparison between this and the initial scan showed improvement in the apical defect with no proximal septal defect.

Discussion

Exercise training is used to treat angina, mainly to improve symptoms by increasing exercise tolerance. This is achieved by a reduction in resting heart rate and a reduction in heart rate and systolic blood pressure at a given exercise level after training.[2] This reduces myocardial oxygen demand. It was hoped that exercise would also improve myocardial oxygen supply, perhaps by encouraging the development of collateral vessels, but there is little evidence of this. Some studies have demonstrated improved ejection fractions or thallium "scores" in individual patients.[3 4] Recent studies have suggested that higher intensity exercise programmes for at least a year can result in real improvements in myocardial function.[5 6] While it is not uncommon for patients to become symptom free during an exercise programme, we know of no other reports of such a dramatic improvement in an exercise tolerance test as we found in this case. Furthermore, the recurrence of exercise induced ST depression after β blockade suggests that β blockade after exercise training had a deleterious effect in a patient who would have been classed as a good responder to β blockade before exercise training.

What is the explanation for the changes that we saw in this patient? Before training thallium scanning identified an area of ischaemia in the most distal region of the septum and apex. This region can be supplied by any of the three major coronary vessels. It is also the region where collateral flow is most commonly seen and where collaterals presumably most readily develop. After training there was an improvement in this defect at the same degree of exercise while at a much higher intensity of exercise a larger defect was seen more proximally in the territory of the left anterior descending coronary artery, with relatively good perfusion at the apex. The most feasible explanation is that the major coronary stenosis lies in the proximal left anterior descending coronary artery, producing the greatest degree of ischaemia in the most distal area in its territory—that is the apex. After training the development of collaterals had improved the supply to this area but at the higher workload a more proximal area in the territory of the left anterior descending artery became ischaemic. Thallium scanning is a more sensitive indicator of ischaemia than exercise induced ST changes.[7] It is not known why some patients with demonstrable ischaemia do not have ST depression. But it is reasonable to assume that the disappearance of exercise induced ST depression in this case was a result of the change in distribution of the ischaemia found on thallium scanning. (We cannot say whether the lack of ST depression implies less significant ischaemia.) If this is the explanation for the changes we saw in our patient, we can only conclude that β blockade after exercise training produced a pattern of ischaemia that resembled the findings before training. With β blockade myocardial oxygen consumption was similar to that achieved before training and the pattern of ST depression was identical to that seen in all three exercise tests before training. We believe that training improved perfusion by a dynamic mechanism that is susceptible to β blockade. If the mechanism is the development of collaterals these cannot function as well under the influence of β blockers. The improvement in treadmill time after training was maintained after β blockade, and this suggests that the peripheral response to training is not inhibited by subsequent β blockade. Although β blockade prolongs exercise time, it is known to reduce maximum myocardial oxygen consumption as measured by the double product (heart rate × systolic blood pressure).[8 9] Also some patients do not respond to β blockade. In our patient we may have demonstrated one explanation for these effects.

A training effect can be achieved in patients on β blockers.[10-12] We believe that this case shows that myocardial perfusion can be improved by exercise training and that the use of β blockers in trained patients may not be desirable. Although we do not wish to overstate the implications of the findings in one patient we feel that they merit further investigation.

Br Heart J 1988;59:263–5

Unusual manifestations of arrhythmogenic right ventricular dysplasia as ventricular fibrillation, atrial paralysis, and hypoexcitable right ventricle

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SUMMARY Ventricular fibrillation occurred in an apparently healthy 19 year old man. The results of non-invasive and invasive studies suggested right ventricular dysplasia. Electrophysiological studies showed atrial paralysis, hypoexcitability of multiple areas of the right ventricle, and inducible poorly tolerated ventricular tachycardia.

Arrhythmogenic right ventricular dysplasia is an unusual disease in which a predominantly right-sided cardiomyopathy is associated with ventricular arrhythmias.[1] Ventricular tachycardia is most commonly observed and often leads to the detection of the cardiomyopathy. We describe an apparently healthy young man who had three unusual manifestations of this disease: ventricular fibrillation as the presenting symptom, atrial paralysis, and hypoexcitable right ventricle.

Case report

A 19 year old man was referred to our hospital on 25 March 1985 for electrophysiological evaluation. His medical history had been unremarkable until 23 February 1985 when he was admitted to Rambam Medical Center with chest discomfort. A few minutes after his arrival he suddenly collapsed and was found to be in ventricular fibrillation which required several DC shocks for termination. There was no history of familial cardiomyopathy, cardiac arrhythmia, or sudden death. Physical examination did not show any abnormalities. Repeated electrocardiograms showed an atrioventricular junctional escape rhythm at a rate ranging from 39 to 48 beats/minute with an incomplete right bundle branch block pattern and a left axis deviation; poor R wave progression was noted in the precordial leads and there were negative T waves in the anterior and lateral leads. No atrial activity could be seen. Chest *x* rays showed cardiomegaly (cardiothoracic ratio of 0·57) without signs of pulmonary congestion. M mode and cross sectional echocardiograms showed diffuse enlargement and hypokinesia of the right ventricle. The right atrium was also considerably dilated with a normally positioned tricuspid valve. The size of the left atrium was normal. The ejection fractions of the right and left ventricle, as determined by radionuclide ventriculography, were 26% and 55% respectively. At cardiac catheterisation, both right and left chamber pressures were within normal range. No "a" waves were present on the right atrial and left ventricular pressure tracings. The right ventricle was globally enlarged and hypokinetic without obvious left ventricular abnormality. The coronary arteries were normal with a dominant left system. The patient was treated with mexiletine (100 mg four times daily) and remained symptom free with frequent ventricular extrasystoles until his transfer to the Tel-Aviv Medical Center.

ELECTROPHYSIOLOGICAL STUDY

This study was performed by standard techniques while the patient was on mexiletine. Attempts to catheterise the coronary sinus to record left atrial activity were unsuccessful. A junctional escape rhythm with a cycle length of 1540–1660 ms was present with an HV interval of 50 ms. No electrical activity could be recorded at multiple right atrial sites. Atrial pacing at these sites, using stimuli of up

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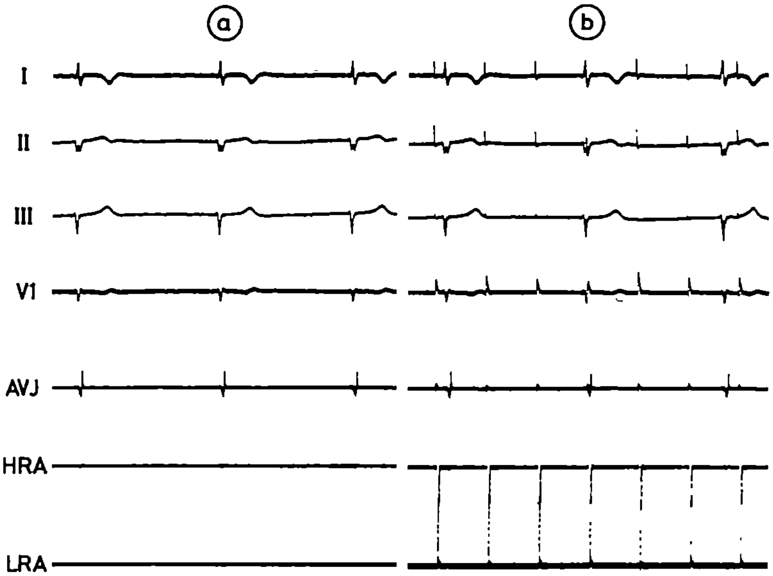

Fig 1 *Electrocardiograms from leads I, II, III, V1 and intracardiac electrograms from the atrioventricular junction (AVJ), high right atrium (HRA), and low right atrium (LRA) showing atrial paralysis. (a) No electrical activity was visible in the HRA and LRA electrograms. (b) Pacing from the HRA with a 20 mA stimulus did not capture the atrium.*

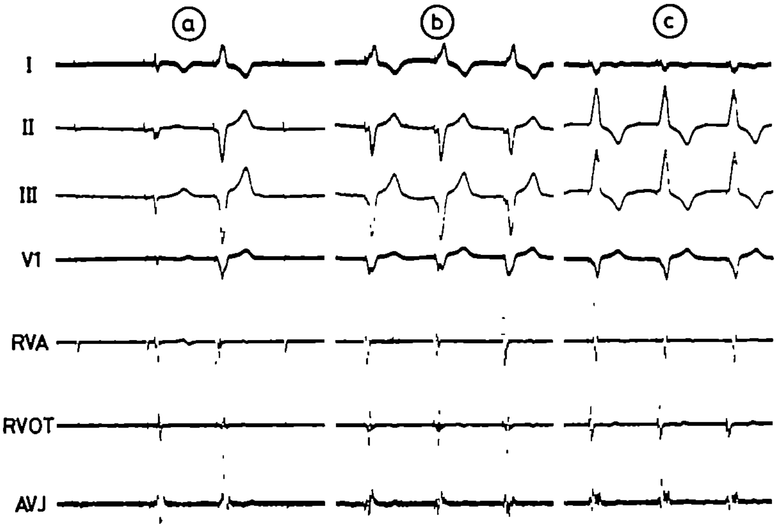

Fig 2 *Electrocardiograms showing hypoexcitability of the right ventricular apex (RVA). (a) Pacing the RVA with a 10 mA stimulus resulted in intermittent ventricular capture. (b) Pacing the RVA with a 20 mA stimulus produced permanent ventricular capture (c) Consistent ventricular pacing was achieved from the right ventricular outflow tract with a 2 mA stimulus.*

to 20 mA in intensity failed to capture the atrium (fig 1). The amplitudes of the right ventricular electrograms were markedly reduced. Pacing at the apical, inferior, and anterior areas of the right ventricle was consistently effective only when stimuli of at least 15 mA were used. In contrast, pacing at the right ventricular outflow tract could be achieved with stimuli as low as 0·6 mA (fig 2). Sustained ventricular tachycardia (cycle length 180–220 ms) with left bundle branch block configuration was induced when two extrastimuli were delivered to the right ventricular outflow tract. This tachycardia was poorly tolerated and required immediate cardioversion for termination. Addition of quinidine (500 mg three times daily) to the continuing mexiletine treatment did not prevent induction of sustained ventricular tachycardia.

FOLLOW UP

Quinidine was discontinued because of considerable QT prolongation. The patient refused the offer of an implantable automatic defibrillator and permanent pacemaker. Two and a half years after discharge he was symptom free on mexiletine alone while showing permanent junctional escape rhythm of about 40 beats/min with frequent and multifocal extrasystoles.

Discussion

Our patient has several of the features that are typical of arrhythmogenic right ventricular dysplasia.[1] In addition, he showed some unusual manifestations of this cardiomyopathy: (a) ventricular fibrillation as the presenting symptom; (b) atrial paralysis, and (c) hypoexcitable right ventricle.

Although ventricular fibrillation has been occasionally noted in arrhythmogenic right ventricular dysplasia,[2] its occurrence as the presenting symptom of this cardiomyopathy in an apparently healthy patient has been reported in only one instance.[3] This suggests that right ventricular dysplasia should be considered as a possible, although most probably rare, cause of sudden cardiac death.

The diagnosis of atrial paralysis (also called "atrial standstill") was based on the following findings: absence of P waves on standard and intracardiac electrograms, lack of atrial excitability, and absence of atrial contraction and atrial pressure changes.[4] As far as we know this is the first report of atrial paralysis associated with right ventricular dysplasia. Because both are rare conditions their association may not have been fortuitous.

The considerable disturbances of right ventricular excitability that we found in our patient have been reported in a patient with Uhl's disease,[5] which is assumed to be an extreme form of right ventricular dysplasia.[6] Although severe forms of right ventricular dysplasia might be expected to produce hypoexcitability of the right ventricle, we do not know of similar findings being reported during electrophysiological studies in patients with this cardiomyopathy.

The association of atrial paralysis with hypoexcitability of several areas of the right ventricle including the apex has important clinical implications, especially when pacemaker implantation is being considered. Endocardial pacing from either the right atrium or the right ventricular apex will not be effective in such patients. Although pacing from the normally excitable right ventricular outflow tract with active fixation electrodes may be considered, the possibility that the progression of the disease will later impair this area[1] suggests that epicardial pacing (ideally from the left ventricle) will be required.

We thank Dr Walter Markiewicz (Rambam Medical Center, Haifa) for performing the cardiac catheterisation of this patient.

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Br Heart J 1988;59:266–9

The surgical treatment of restrictive cardiomyopathy in pseudoxanthoma elasticum

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SUMMARY A patient with pseudoxanthoma elasticum presented in pulmonary oedema with restrictive left ventricular cardiomyopathy caused by calcified endocardial bands that were confirmed on echocardiography and at catheterisation. The bands were resected as far as possible and the involved mitral valve was replaced by a heterograft. A year later calcification of the heterograft forced its replacement by a St Jude prosthesis. Relief of symptoms has been good in the medium term.

Case report

A 27 year old white man, known to have pseudoxanthoma elasticum, presented with a rapidly progressive nine month history of exertional dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, and the striking symptom of exertional haemoptysis. Over the nine month period his exercise tolerance had decreased from that of an active amateur footballer to being unable to walk more than one hundred yards on the flat.

Physical examination showed the classic skin lesions of pseudoxanthoma elasticum—yellow pseudoxanthomatous plaques, mainly in the neck region. There was evidence of congestive cardiac failure, with a sinus tachycardia, a loud left ventricular third heart sound, bilateral basal crepitations, jugular venous pressure raised 3–4 cm with a deep "y" descent, an enlarged pulsatile liver, and oedema of the legs. The electrocardiogram showed no abnormality and in particular the QRS complexes and T waves were normal. The chest *x* ray showed considerable calcification within the cardiac outline—in particular in the region of the left ventricle (figure). The classic appearances of pulmonary oedema were present. Cross sectional and M mode echocardiography showed several abnormal features (table 1). The left ventricular endocardium was markedly thickened, particularly in the posterior wall region. There was "flattening" of the left ventricular posterior wall diastolic motion, although this could not be assessed quantitatively. There appeared to be diastolic restriction of left ventricular filling. The mitral valve E–F slope was at the lower limit of normal and mitral valve excursion was reduced. Left ventricular systolic function appeared to be normal, as shown by a normal ejection fraction and left ventricular fractional shortening. Left ventricular systolic and end diastolic internal dimension were within normal limits. The left atrium was markedly enlarged, in keeping with restriction of diastolic filling of the left ventricle in the absence of mitral stenosis. There was minor prolapse of the anterior mitral leaflet. The pericardium appeared to be of normal thickness. The right ventricle appeared to be normal.

The clinical and echocardiographic findings suggested a diagnosis of a restrictive left ventricular cardiomyopathy secondary to pseudoxanthoma elasticum. To obtain a definitive diagnosis, cardiac catheterisation was undertaken. Table 2 gives the right and left heart pressures obtained before angiography. The left ventricular end diastolic pressure was markedly raised at 25–30 mm Hg. The pulmonary artery and right ventricular pressures were also raised, although the right ventricular end diastolic pressure was normal. The pulmonary artery wedge pressure was raised with considerable "x" and "y" descents. Right atrial pressures were normal. There were no valve gradients. Left ventricular angiography showed a heavily calcified left ventricular endocardium with overall reduction in left ventricular contractility and a prolonged diastolic phase. There was mild mitral regurgitation. The

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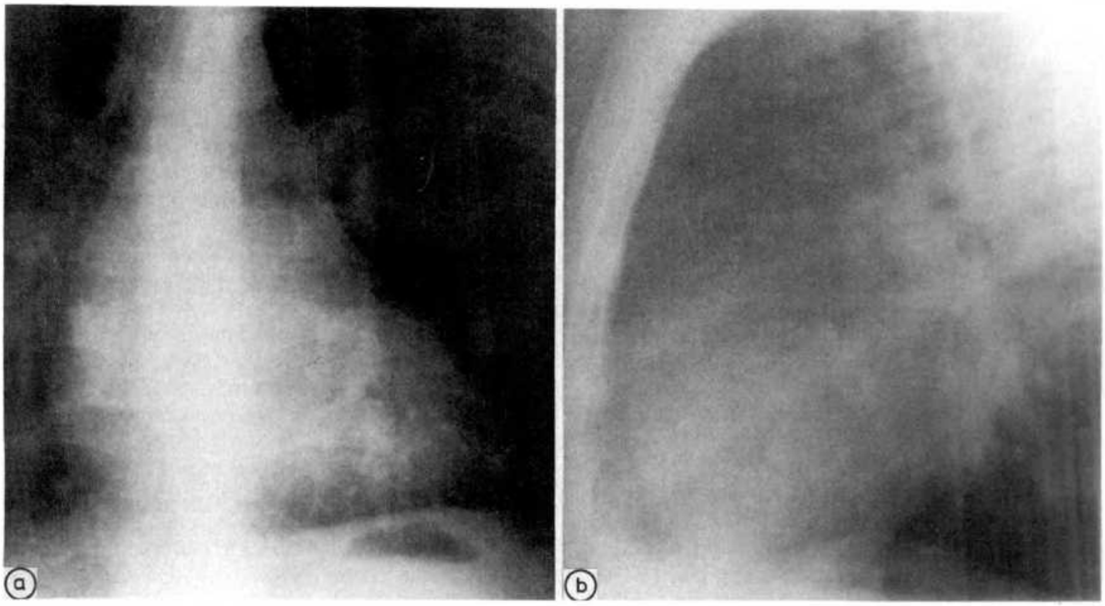

Fig *Chest x rays from posterior-anterior (a) and lateral views (b) showing calcification in the region of the left ventricle.*

right ventricle contracted normally. Coronary arteriography revealed a solitary stenosis of 40% beyond the first septal branch of the left anterior descending coronary artery. These findings confirmed our diagnosis of a restrictive cardiomyopathy solely affecting the left ventricle. The only cause appeared to be the extensive, but discrete, bands of endocardial calcification extending into the myocardium which were theoretically amenable to resection. In view of his age and rapidly deteriorating condition it was decided to attempt surgical resection.

At operation the lining of the left ventricle was thickened, fibrous, and mainly calcified, although there seemed to be three distinct ridges of calcified tissue along the posterior wall; the last of these was particularly restricting dilatation of the left ventricle. The calcification was friable and went deeply into the myocardium. The mitral valve leaflets were normal, but the chordae were inserted into calcified papillary muscles. The calcification in the posterior wall and to some extent in the two lateral walls was excised as far as possible.

The mitral valve was replaced with a size 31 Carpentier-Edwards heterograft in view of the papillary muscle involvement. The coronary artery lesion was not considered to be haemodynamically important.

After operation his general condition improved

Table 1 *Echocardiographic features before operation*

Feature		*Normal limits*
Mitral valve E–F slope	53	(50–120 mm/s)
Mitral valve excursion	1·7	(2·0–2·5 cm)
Aortic root diameter	2·9	(2·0–3·7 cm)
Aortic valve cusp separation	2·0	(1·6–2·6 cm)
LA internal dimension	5·9	(1·9–3·8 cm)
Septal thickness (diastole)	1·2	(0·7–1·1 cm)
Posterior LV wall thickness (diastole)	1·8	(0·7–1·1 cm)
LV internal dimension (systolic)	2·6	(2·5–4·1 cm)
LV internal dimension (end diastolic)	4·2	(3·5–5·6 cm)
Cubed formula LV stroke volume	57	(55–95 ml)
Ejection fraction	77	(65–75%)
LV fractional shortening	0·38	(0·28–0·41)

LA, left atrium; LV, left ventricle.

Table 2 *Catheter findings before and after operation*

Vessel or chamber	*Pressure (mm Hg)*	*Mean or end diastolic pressure*
	Before operation	
Right atrium	a = 2·5 v = 0 x = −5 y = −1	Mean = −1·5
Right ventricle	90/0	EDP 2–5
Pulmonary artery	90/30	Mean = 50
PAWP	a = 30 v = 35 x = 15 y = 10	Mean = 20
Left ventricle	110/0	EDP 23–30
Aorta	110/60	Mean = 85
	After operation	
Right atrium	a = −1 v = 1 x = −3 y = −3	Mean = −1
Right ventricle	40/−6	
Pulmonary artery	32/12	Mean = 20
PAWP	a = 10 v = 11 x = 9 y = 8	Mean = 10
Left ventricle	120/−5	EDP 10
Aorta	120/70	

PAWP, pulmonary artery wedge pressure.

markedly with disappearance of both his abnormal symptoms and physical signs. He was discharged home two weeks after operation. In view of the inherent danger of prescribing anticoagulants to patients with pseudoxanthoma elasticum he was not given anticoagulants. Three months later he was well and had no symptoms or abnormal physical signs. Echocardiography confirmed his clinical improvement. Posterior left ventricular wall motion was normal and there did not seem to be any restriction of diastolic left ventricular filling. Cardiac catheterisation was repeated. Table 2 shows the considerable improvement in left ventricular end diastolic pressure, which had fallen to 10 mm Hg. Pulmonary artery pressure was correspondingly reduced. Left ventricular angiography showed an overall improvement in contractility.

He subsequently remained well for one year but later presented with a two month history of dyspnoea and orthopnoea. On examination he was once again found to be in pulmonary oedema with bilateral basal crepitations, a sinus tachycardia, and loud third heart sound. There was a loud mid-diastolic murmur at the apex. Cross sectional echocardiography showed that the mitral heterograft was thickened and rigid. The left ventricular filling rate was reduced. Overall left ventricular contractility appeared to be normal. Cardiac catheterisation was again repeated. The left ventricular end diastolic pressure was within normal limits at 5 mm Hg. There was a gradient of 19 mm Hg across the mitral prosthesis. Left ventricular angiography confirmed the continued improvement in left ventricular contractility. The mitral heterograft appeared rigid and immobile. These findings suggested that the return of his symptoms was related to stenosis of the mitral heterograft and not to a recurrence of the restrictive cardiomyopathy.

Further operation was indicated and the mitral heterograft was replaced with a St Jude prosthesis and treatment with anticoagulants was started and continued. His recovery was uneventful and associated with complete loss of all his symptoms. At follow up over the next year he was free of symptoms and leading a normal life.

Discussion

The rare condition of pseudoxanthoma elasticum, first described by Rigal in 1881, is inherited as an autosomal recessive.[1] It is a multisystem disorder affecting the skin, mucous membranes, eyes, blood vessels, and heart. The pathogenesis is poorly understood, but there is an important defect in the metabolism and subsequent synthesis of elastic fibres. The resulting elastic tissue, which is abnormal, calcifies and degenerates.[2]

Cardiovascular complications are well documented and include angina pectoris caused by premature coronary artery disease,[3] with sudden death from acute myocardial infarction,[4] hypertension,[5] premature peripheral vascular disease,[6] mitral valve prolapse,[7] and congestive cardiac failure. The case we describe had mild coronary artery disease, but congestive cardiac failure was the predominant cardiovascular complication. This has been reported in up to 70% of cases. The aetiology is multifactorial with hypertension, mitral valve disease, myocardial ischaemia,[8] and direct endocardial involvement[9] implicated, although the exact manner in which the latter leads to congestive cardiac failure is poorly understood. In the case we describe diffuse endocardial fibrosis and calcification resulted in the development of restrictive cardiomyopathy. Restrictive cardiomyopathy has only been described on one previous occasion in pseudoxanthoma elasticum.[10] The characteristic echocardiographic features of a restrictive cardiomyopathy have been described in other infiltrative cardiac disorders including primary cardiac amyloidosis.[11] These features include a normally sized ventricular cavity with normal ventricular systolic function, "flattening" of ventricular posterior wall motion,[12] diastolic restriction of ventricular filling, and reduction in the E–F slope of the mitral valve. There is usually considerable endocardial thickening, and the left atrium is enlarged in the absence of mitral valve disease. In our case all of these features affected the left ventricle.

The standard 12 lead electrocardiogram is usually non-specific, although T wave changes and conducting disturbances have been recorded. The chest *x* ray is similarly not usually a help in establishing the diagnosis, but calcification was a striking feature in our patient. There is little information on the echocardiographic features of cardiac involvement in pseudoxanthoma elasticum, and we believe our report to be the first to describe echocardiographic features of a restrictive cardiomyopathy in this condition.

Cardiac surgery has rarely been undertaken in pseudoxanthoma elasticum, although triple coronary artery bypass grafting has been performed in an 18 year old girl with a seven year history of angina pectoris.[13] We believe that our case is the first in which relief of a restrictive cardiomyopathy by limited resection of the calcified bands has been attempted. The duration of such palliation cannot be certain but in the medium term relief of symptoms has been good. A Carpentier-Edwards mitral heterograft was initially inserted in this case, in the hope that lifelong anticoagulant treatment could be avoided, because of the danger of gastrointestinal bleeding in this condition. Valvar heart disease such as mitral calcification, mitral and tricuspid valve stenosis, and aortic insufficiency, although rare, have all been reported.[14 15] It therefore seems likely that the rapid onset of heterograft calcification in our patient was directly related to the disease process. Thus despite the obvious risks of anticoagulation, a mechanical prosthesis is preferable to a heterograft.

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Br Heart J 1988;59:270–4

Correspondence

Early treatment of unstable angina in the coronary care unit: a randomised, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both

Sir,
The study on the early treatment of unstable angina in the coronary care unit by the Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) Research Group (1986;56:400–13) requires comment.

(a) *The study was terminated too soon*

The HINT study suggested that although the addition of nifedipine to routine treatment could be "detrimental" to patients not previously on β blockers, the addition of nifedipine to existing treatment with β blockers was "beneficial". The trial was ended too early, probably because an interim analysis suggested that the risk of myocardial infarction was greater in patients assigned to nifedipine. The reason for this decision does not appear in the discussion and is poorly documented in the appendix. The analysis only demonstrates the well known fact that an unplanned interim analysis without correction of α error may produce a significant difference.

(b) *Imbalance in the monotherapy groups and the inability of the investigators to differentiate between onset of acute myocardial infarction and unstable angina*

When the Steering Committee made its decision it had not been informed of the clear imbalance of risk at baseline between the study groups. The authors admit that the onset of myocardial infarction in patients presenting with symptoms of unstable angina is uncertain and that they may have miscalculated by more than six hours. Under clinical conditions the use of enzyme determinations for the diagnosis of myocardial infarction is an inaccurate and, at times, an inconsistent indicator of infarction. The higher incidence of myocardial infarctions in the group assigned to nifedipine monotherapy may be explained by the possible (pre) existence of myocardial infarction; and in these circumstances it would be incorrect to use the term "detrimental". Indeed, the recent TRENT study on a much larger group of patients with confirmed acute myocardial infarction did not show any "detrimental" effects of nifedipine.[1]

Later in the HINT study it was found that 43 patients had already had an infarction before treatment but these cases were not excluded even though they no longer fulfilled the inclusion criterion for "unstable angina" and the therapeutic aim, "treatment of unstable angina pectoris", could no longer be achieved. The uniformity of all the groups was not examined and a table showing these data should be published so that the comparability of the treatment groups and the individual centres can be checked.

(c) *Baseline risk differed considerably in the various treatment groups*

The "high baseline risk" of recurrent ischaemia or myocardial infarction within 48 hours was 18% in the nifedipine group and 5% in the metoprolol group. An attempt was made to overcome this imbalance by logistic regression. Since angiography was not available to assess the severity of the underlying coronary artery disease and there is no information on the distribution of these high risk patients among the participating centres, further analysis of these groups on the basis of equal prior risk and equal prior treatment is indicated.

(d) *Nifedipine responders were excluded but metoprolol responders were not*

Patients taking nifedipine maintenance treatment on admittance were excluded whereas those on β blockade maintenance treatment were not. Both medications were probably prescribed for the same indication and it is likely that the exclusion of patients on nifedipine maintenance treatment probably unbalanced the study in favour of metoprolol.

(e) *The term "placebo" is misleading*

"Placebo" suggests that only a placebo was given. In part A of the analysis placebo is the term used for "conventional" treatment and no details of this are given; however, 87% received long acting nitrates, 76% anticoagulants, and 40% diuretics. Is it possible that a combination of these medications led to a pronounced hypotensive state in those assigned to monotherapy with nifedipine. Further details of the influences of concomitant medication are required, and we need to know the distribution of this concomitant treatment, especially in those patients who progressed to myocardial infarctions. In part B the term "placebo" group indicates treatment with metoprolol and "nifedipine" placebo.

(f) *Confidence limits in patients not pretreated with β blockers are too wide and differences in efficacy so small that statements like "beneficial" and "detrimental" indicate trends rather than statistically significant differences*

In general combined treatment with nifedipine and β blockers had a positive effect both in the pretreatment and no pretreatment groups. This supports the current practice of treating patients with unstable angina with a combination of β blocker and nifedipine. The authors should state this fact instead of branding nifedipine as "detrimental".

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Reference

1 Wilcox RG, Hampton JR, Banks DC, *et al*. Trial of early nifedipine in acute myocardial infarction: the TRENT study *Br Med J* 1986;293:1204–8.

This letter was shown to the authors, who reply as follows:

Sir,

The issues raised by Weihrauch *et al* are covered in an article that is to appear in the *European Heart Journal*. Our answers are summarised below.

(a) *The study was terminated too soon*

The decision to terminate the study was taken by the Executive Committee and was based on the unanimous recommendation of the Policy Advisory Board. The interim data on which this recommendation was based are given in appendix I of our paper. Interim data such as these are not usually disclosed for trials that have been terminated ahead of time.

Even in retrospect, we regard it inconceivable that we could have reached any other decision about nifedipine monotherapy, even if the final effect estimates had been available. In terms of efficacy the distinction between "no effect" and "negative effect" (or equivalently, "detrimental effect") is of no real importance. On the other hand, we would view it as unethical to continue such a trial in the face of a negative trend just to establish the distinction between "no effect" and "negative effect" beyond reasonable doubt. Decisions about the other treatments might have been different had a more detailed analysis been available to us.

As regards Weihrauch *et al's* comments on "statistical significance" and the possibility of an α error, we must point out that as we do not subscribe to the traditional notion of calculating p values and declaring differences to be statistically significant or not, the issue of adjustment of p values in the context of multiple tests therefore does not arise. In fact the positive effect of nifedipine in patients on previous maintenance treatment with a β blocker was the only difference that was statistically significant. Therefore, when Weihrauch *et al* state that "an unplanned interim analysis without correction of α error may produce a significant difference" they suggest that this positive effect of nifedipine may be spurious.

(b) *Differentiation between acute myocardial infarction and unstable angina*

For the 43 cases with myocardial infarction with a probable onset before randomisation, we have (in keeping with current practice) adhered to the intention to treat principle. This approach accords with ordinary clinical diagnosis, which is by definition based on past and present symptoms and not on those that may or may not develop in the future. All patients entered in the HINT, including these 43 patients, were diagnosed as having unstable angina based on symptoms and signs present just before randomisation; they all had enzyme values below twice the upper limit for normal. Thus patients who were later classified as (probably) having the onset of infarction before randomisation also satisfied the HINT definition of unstable angina.

The TRENT study was of patients with symptoms and signs of acute myocardial infarction. Whether nifedipine does or does not promote the development of myocardial infarction in patients with symptoms and signs of unstable angina cannot be inferred from a study with patients presenting with symptoms and signs of acute myocardial infarction, although there is considerable overlap between the clinical pictures at issue. In any case the TRENT data confirm that in acute myocardial infarction no therapeutic benefit can be expected from nifedipine.

(c) *Differences in baseline risk*

The baseline risk for recurrent ischaemia or myocardial infarction within 48 hours was estimated for each individual patient by a logistic model. The apparent imbalance in baseline risk was corrected for (by stratified analysis) in the adjusted effect estimates presented in table 5 of the HINT paper. This comparison within strata of equal baseline risk reduced the observed negative effect of nifedipine monotherapy from 1·28 (that is an increase of 28%) to 1 15 (an increase of 15%). Subsequent findings at angiography were not and cannot be used as baseline characteristics for acute treatment at hospital admission, because the clinician must decide on early treatment without knowing the angiographic findings. We believe that the analysis of clinical trial data should reflect the clinical situation under investigation, and hence we have not used findings of predischarge angiography. The angiographic data are given in the article that is to appear in the *European Heart Journal.*

(d) *Exclusion of patients on maintenance treatment with nifedipine*

Giving nifedipine to patients who were already taking nifedipine when unstable angina developed is not an appropriate therapeutic action. Instead, the clinician could add β blockade. The latter option was not investigated in HINT because we expected that only a few of these nifedipine non-responders without a contraindication for a β blocker would present, as nifedipine had only been recently introduced when HINT was designed in 1980. Thus we did not exclude nifedipine responders, rather we omitted a β blocker/placebo comparison in nifedipine non-responders. Therefore, there is no argument for the suggestion that the exclusion of patients already on nifedipine unbalanced the study in favour of metoprolol.

(e) *Use of the term "placebo"*

Our use of the term "placebo" accords with convention—that is a placebo for the drug under investigation, with rules for concomitant medication stipulated in the study protocol. The HINT data indicate that previous medication, which was continued in most instances, was not related to prognosis. Therefore, it is highly unlikely that the observed negative trend for nifedipine monotherapy was caused by interaction with other medications such as long-acting oral nitrates.

(f) *Width of the confidence intervals*

We believe that the wide confidence intervals preclude definite conclusions being based on the HINT data alone. Nevertheless, the HINT data do not support Weihrauch *et al*'s proposal that combination treatment is the treatment of choice on hitherto untreated patients. Whether the HINT data are conclusive enough to discourage the use of a fixed combination as the initial treatment is another matter. None the less, they do support the current practice of adding nifedipine to the regimen when the initial β blocker fails.

We have stated that the HINT findings "suggest that in patients not on previous maintenance treatment with β blocker . . . nifedipine may be detrimental". The word "detrimental" was used to reflect the possibility of negative efficacy. Our conclusion was (and still is) that the HINT data virtually exclude a major preventive effect of nifedipine monotherapy in unstable angina (as defined in HINT).

J Lubsen, JGP Tijssen, OS Miettinen for the HINT Research Group,
Thoraxcentre, Clinical Epidemiology Unit,
Erasmus University,
Rotterdam,
The Netherlands.

Reference

1 Tijssen JGP, *et al.* Nifedipine and metoprolol in suspected unstable angina: the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). *Eur Heart J* 1987;8(suppl H):1–104.

Suppressor T lymphocyte function in patients with idiopathic congestive cardiomyopathy

Sir,
Dr Lowry and her colleagues reported (1987;57:458–61) that they were unable to detect a defect in T lymphocyte function in their patients with dilated cardiomyopathy. At first sight this might appear to contradict our results from patients with dilated cardiomyopathy studied in Kenya where we found that about half the patients had a high helper/suppressor (OKT4/OKT8) T lymphocyte subset ratio.[1] This apparent difference may be explicable, however. All our patients with a high helper/suppressor ratio were seen within three months of the onset of their symptoms (Lowry *et al* do not state the duration of illness in their patients) and we felt that the higher ratios merely represented an active immunological reaction as part of a chronic or subacute myocarditis.

As the myocarditis "burns out", the helper/suppressor ratio will return to normal. At this later stage there may be no immunological changes to detect. Furthermore, the high helper/suppressor ratios in our patients were caused by an increased number of helper cells rather than a significant reduction of suppressor cells, so that the changes are not likely to be non-specific and due to heart failure alone.

I would agree with Lowry *et al* that there is unlikely to be a permanent defect in T lymphocyte function that is specific to these patients but this does not rule out the possibility that an immunological reaction (which may be excessive) is part of the early pathogenesis of dilated cardiomyopathy. And this may be detected only if the patients are studied early after the onset of their illness.

John Sanderson,
Musgrove Park Branch,
Taunton and Somerset Hospital,
Taunton,
Somerset TA1 5DA.

Reference

1 Sanderson JE, Koech D, Iha D, Ojiambo HP. T-lymphocyte subsets in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1985;55:755–8.

Sir,
Lowry *et al* suggested that the defect in T lymphocyte function that they found in patients with idiopathic congestive cardiomyopathy may be a non-specific reduction that is associated with heart failure rather than with the cardiomyopathy itself. We too reached a similar conclusion in a recent paper[1]: we found that the ratio of helper (T4) to suppressor (T8) lymphocytes (labelled by monoclonal antibodies) was higher because of a decrease in the percentage of T8 lymphocytes in patients with idiopathic congestive cardiomyopathy and ischaemic cardiopathy. The fall in T8 lymphocytes was more pronounced (and statistically significant) in patients with idiopathic cardiomyopathy than in patients with ischaemic cardiopathy with heart failure.

We also found that the ratio of helper T lymphocytes to responder T lymphocytes determined by in vitro culture was different from the ratio in vivo.

We believe that heart failure may impair T lymphocyte function, but this does not exclude the possibility of immunological dysfunction in idiopathic congestive cardiomyopathy.

R N Sachs,
J Lanfranchi,
Hôpital Avicenne,
125 rue de Stalingrad,
93008 Bobigny,
France.

Reference

1 Sachs RN, Hatron PY, Saizy C, Lanfranchi J. Etude des sous populations lymphocytaires T par les anticorps monoclonaux au cours des cardiomyopathies dilatées primitives et alcooliques. *Ann Med Interne (Paris)* 1985;136:229–32.

These letters were shown to the authors, who reply as follows:

Sir,
We note with interest the comments of Dr Sanderson and Dr Sachs and Dr Lanfranchi.

Our study was essentially a quantitative assessment of suppressor cell function, prompted by reports of impaired function which might, in some way, allow a sequence of events terminating in congestive cardiac failure.[1 2] We have previously reported a quantitative study of T cell populations in three groups: eight patients with congestive cardiomyopathy, eight patients with heart failure caused by coronary disease, and eight normal controls.[3] There was no significant difference in the ratio of helper/suppressor cells between the groups, although there was a tendency for both heart failure groups to have higher ratios. This was due to both an increase in helper cells and a decrease in suppressor cells in both patient groups, but none of these differences was significant. These results suggested to us that any defect of suppressor cells must lie in abnormal function rather than in reduced numbers but we have failed to demonstrate a specific abnormality of suppressor cell function in the heart failure of congestive cardiomyopathy. We agree with Sanderson, however, that an immunological abnormality may be transient and detectable only in the early stage of congestive cardiomyopathy. All of our patients in both studies had been known to have congestive cardiomyopathy for more than three months.

P J Lowry,
M D Gammage,
R A Thompson,
W A Littler,
Department of Cardiovascular Medicine,
East Birmingham Hospital,
Bordesley Green East,
Birmingham B9 5ST.

References

1 Fowles RE, Bieber CP, Stinson EB. Defective in vitro suppressor cell function in idiopathic congestive cardiomyopathy. *Circulation* 1979;59:483–91.
2 Eckstein R, Mempel W, Bolte HD. Reduced suppressor cell activity in congestive cardiomyopathy and in myocarditis. *Circulation* 1982;65:1224–9.
3 Lowry PJ, Thompson RA, Littler WA. Cellular immunity in congestive cardiomyopathy: the normal cellular immune response. *Br Heart J* 1985;53:394–9.

Notices

British Cardiac Society

The Annual General Meeting for 1988 will take place in Belfast on 23 and 24 March 1988, and the closing date for receipt of abstracts was 4 January 1988.

Cardiovascular intervention

A workshop on coronary angioplasty and other related procedures will be held at the London Hospital on 28 and 29 April 1988. Inquiries to Dr M T Rothman, The London Hospital, London E1 1BB.

Pacing and electrophysiology

The annual scientific meeting of the North American Society of Pacing and Electrophysiology will take place in Los Angeles on 12 to 14 May 1988. Inquiries to NASPE, 13 Eaton Court, Wellesley Hills, MA 02181, USA.

Correction

Ventricular defibrillation: the Belfast experience. *G W N Dalzell, S R Cunningham, C M Wilson, J D Allen, J Anderson, A A J Adgey*—We regret that two errors were introduced into this article published in the November issue (volume 58: pages 441–6). On page 442 the second sentence of the section entitled "Prognosis of patients in ventricular fibrillation" should have read "When ventricular fibrillation occurred *less* than four hours after the onset of symptoms (these were mainly patients with acute myocardial infarction), approximately 80% were alive three years after the initial episode." Also on page 442 the last sentence in the left hand column should have read "In 1983 we looked at 125 patients with ventricular fibrillation."

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Br Heart J 1988;59:275–9

Ten year follow up of patients with single vessel coronary artery disease that was suitable for percutaneous transluminal coronary angioplasty

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SERGE BRIANÇON, MICHEL CUILLIÈRE, ETIENNE ALIOT,
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FRANÇOIS CHERRIER

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SUMMARY The 10 year outcome of patients with single vessel coronary artery disease who underwent coronary angiography more than 10 years before and who would have been potential candidates for percutaneous transluminal coronary angioplasty had it been available then is reported. Long term follow up data were obtained in 96 (91 men, five women; mean age 48 years) of 105 consecutive patients with single vessel coronary artery disease (>70% stenosis), judged suitable for coronary angioplasty. Fifty patients had coronary bypass surgery within six months of catheterisation (surgical group) and 46 were treated medically (medical group). At entry to the study more patients in the surgical group had unstable angina, but fewer had a previous history of myocardial infarction. Ten year survival was 91% and remained excellent in all the subsets analysed. Moreover, the quality of life of these patients was good. Over the 10 year follow up, 16 (36%) of the patients treated medically and 13 (26%) in the surgical group were admitted to hospital because of cardiovascular events (including late coronary surgery in four of the patients treated medically). Lastly, 54/69 (78%) of the patients who were employed before catheterisation resumed work and 29 (42%) were still employed 10 years later.

Although these data must be interpreted with care because of the limitations inherent in all retrospective studies, it appears that the long term results of conventional medical or surgical treatment are excellent in patients with single vessel coronary artery disease in whom percutaneous transluminal coronary angioplasty is now an option.

Percutaneous transluminal coronary angioplasty is now widely used to treat coronary artery disease—more than 70 000 procedures were performed in the United States in 1984.[1] Though the indications of the procedure have been extended considerably over the past five years, most patients undergoing percutaneous transluminal coronary angioplasty still have single vessel disease. To date, however, there is no clear cut evidence that percutaneous transluminal coronary angioplasty is better than medical treatment or coronary artery surgery in such patients. Because there is no continuing prospective randomised study of percutaneous transluminal coronary angioplasty compared with coronary artery bypass surgery or medical treatment in patients with single vessel disease, retrospective studies must be used to provide standards for the evaluation of the results of the new treatment. We have studied the long term outcome of patients with single vessel disease who underwent coronary arteriography ten years before and who would have been suitable candidates for percutaneous transluminal coronary angioplasty had the technique been available then.

Patients and methods

INCLUSION CRITERIA

The study population was chosen from the coronary

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Accepted for publication 30 September 1987

angiographic registry of our centre. The coronary angiograms of a consecutive series of 141 patients admitted to our department from April 1972 to March 1976 who had a subtotal stenosis of the luminal diameter (>70%) of one of the three main coronary arteries, without involvement of the other coronary arteries (<50% stenosis), were reviewed by two independent observers who were experienced in coronary angioplasty. Only those patients who had a stenosis that was judged to be suitable for percutaneous transluminal coronary angioplasty were included—that is a single stenosis, concentric or eccentric, not calcified, no longer than 1·5 cm, not significantly affecting a side branch and sited in segments 1, 2, 3 (right coronary artery), 12, 13 (left anterior descending), or 18, 19, 20 (left circumflex) of the coronary arteries as defined by the Coronary Artery Surgery Study.[2]

FOLLOW UP

The long term outcome of the patients was studied by a simple questionnaire sent to all patients who were presumed to be alive. Furthermore, information was obtained from the patients' physicians and cardiologists. When no information was obtained by these different methods, we contacted the registries in the patients' birthplaces to check whether their death had been registered; however, a patient was believed to be alive only if direct information was obtained from the patient, his family, or his physicians. Patients lost to follow up during the follow up period were included in the study up to the time they were last known to be alive.

DATA ANALYSIS

Survival rates from the time of coronary angiography were calculated by life table methods. Baseline variables in the medical and surgical groups were compared by χ^2 tests (Yates' correction when appropriate) for discrete variables and Student's *t* tests for continuous variables.

Results

POPULATION

Of the 2265 patients catheterised during the study period, 141 (6 2%) had a subtotal (>70%) stenosis in a single coronary artery. Of these, 36 were excluded upon review of the coronary angiogram for the reasons listed in table 1. The table gives only the main exclusion criterion for each patient.

One hundred and five consecutive patients had a single vessel stenosis that was judged to be suitable for percutaneous transluminal coronary angioplasty. Nine (8 6%) of these, four of whom were foreigners, were lost to follow up. The study population therefore comprised 96 patients (91 men and five women; mean (SD) age 47·9 (7·9) years). Fifty patients had coronary artery surgery (internal mammary artery graft 35, saphenous vein graft 15) within six months of catheterisation. Forty six patients were treated medically, four of them underwent late coronary artery surgery 6–9 years after catheterisation.

Table 1 *Reasons why patients were excluded when the coronary angiogram was reviewed*

Angiographic characteristic	*Patients (No)*
Near obstruction	10
Distal narrowing	6
Additional distal narrowing	5
Narrowing at bifurcation	5
Calcified deposits	4
Length of narrowing	3
Superimposed coronary artery spasm	3

Table 2 gives the main baseline clinical and angiographic characteristics of the two groups. In the surgical group more patients presented with unstable angina pectoris (25 (50%) *vs* 9 (20%), p < 0·01), whereas in the medical group more patients were symptom free or had atypical chest pain (15 (33%) *vs* 3 (6%), p < 0·01). Similarly, more medically treated patients had had a previous episode of myocardial infarction (21 (46%) *vs* 9 (18%), p < 0·01). Left ventricular ejection fraction could not be measured in five medically treated and seven surgically treated patients (no left ventricular angiogram in one and four patients respectively, and left ventricular angiogram unsuitable for determination of ejection fraction in four and three patients respectively); three (7%) patients in the surgical group and eight (20%) in the medical group had an ejection fraction below 0·50 (NS). The left anterior descending artery was most commonly affected in both treatment groups.

TEN YEAR SURVIVAL

For the whole study population ten year actuarial survival was 91%. In four of the nine patients who died during follow up the cause of death was directly related to ischaemic heart disease; two patients died of cancer and the cause of death was unknown in three patients. Furthermore, ten year survival was excellent in all of the subsets studied. Ten year survival was 91% for the medical group and 90% for the surgical group (fig 1). When analysed according to the vessel affected (fig 2) survival was 91% for left anterior descending stenoses (medical group 93%, surgical group 90%), 89% for right coronary artery stenoses (90% in both treatment groups), and 92% in patients with stenoses of the left circumflex (medical group 90%, surgical group 100%). In patients with

Table 2 *Baseline characteristics in patients treated medically or surgically*

Variable	*Medical treatment (n = 46)*	*Surgical treatment (n = 50)*	*p value*
Sex:			
Male	44	47	NS
Female	2	3	
Mean age (SD) (year)	47 (7)	49 (9)	NS
Mean duration of symptoms before coronary angiography (SD) (mnth)	10 5 (11)	11 5 (21)	NS
Reason for coronary angiography:			
Unstable angina	9	25	
Stable angina	22	22	0 01
Atypical chest pain/abnormal rest ECG	15	3	
Previous myocardial infarction	21 (46%)	9 (18%)	0 01
Location of coronary artery stenoses:			
Left anterior descending	27	38	
Right coronary artery	9	9	NS
Left circumflex	10	3	
Ejection fraction <0 50	8/41 (20%)	3/43 (7%)	NS

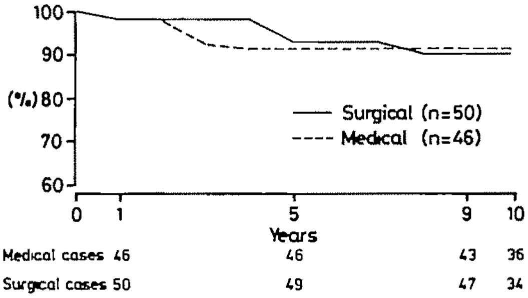

Fig 1 *Ten year actuarial survival of potential candidates for percutaneous transluminal coronary angioplasty according to treatment. M, medical group; S, surgical group.*

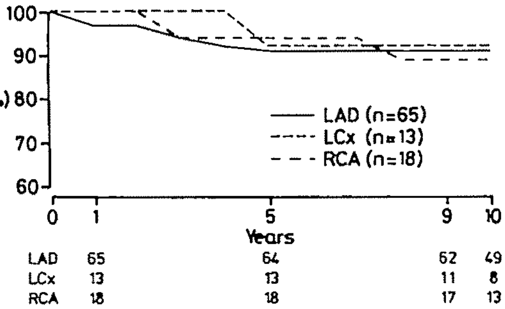

Fig 2 *Ten year actuarial survival of potential candidates for percutaneous transluminal coronary angioplasty according to affected coronary artery. LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery.*

angina at the time of catheterisation, ten year survival was 90% (89% for surgically treated patients and 90% for medically treated patients); when analysed according to the vessel involved, all subsets of patients had an 86% or higher survival at ten years.

Lastly, ten year survival in patients with previous myocardial infarction was 93%–100% in the surgical group (n = 9) and 90% in the medical group (n = 21).

Table 3 *Quality of life at follow up*

Variable	*Medical treatment*	*Surgical treatment*
Subjective assessment:		
Very well/well	14	20
Fair	22	16
Poor	1	2
Better	17	27
Same	12	10
Worse	7	1
Chest pain at follow up.		
None	11	17
Moderate	16	11
Severe	13	11
Hospital admission during follow up:		
No	22	18
Cardiovascular	14 (CABG = 4)	10
Other	3	10
Treatment at follow up		
None	1	1
Antianginal drugs	28 (76%)	18 (47%)
Anticoagulant drugs	24 (65%)	31 (82%)

Some of the patients answered only part of the questionnaire

QUALITY OF LIFE

The quality of life was assessed in the patients who answered all or part of the questionnaire (40 patients in the medical group and 39 patients in the surgical group (table 3).

At follow up most patients felt well: 14/37 (38%) of the medically treated and 20/38 (53%) of the surgically treated patients felt well or very well. Twenty seven (71%) of the surgically treated patients and 19 (47%) of the medically treated patients reported an improvement after catheterisation. Angina pectoris is always difficult to assess by means of a questionnaire; however, 11 (28%) of the patients in the medical group and 18 (46%) in the surgical group did not complain of chest discomfort.

During the 10 year follow up period, 14 (36%) patients in the medical group and 10 (26%) patients in the surgical group were admitted to hospital because of cardiovascular events. In the medical

Table 4 *State of employment of patients treated medically or surgically*

	Medical group	*Surgical group*
Employed before coronary angiography	36	33
Return to work after coronary angiography or surgery	30 (83%)	24 (73%)
Still working at follow up	19 (53%)	10 (30%)

group four (10%) patients underwent late coronary artery bypass surgery 6–9 years after the initial catheterisation; three (8%) additional patients were admitted to hospital for myocardial infarction; the other reasons for hospital admission were angina, cerebrovascular accident, syncope, and severe haematoma in a patient treated with oral anticoagulants. In the surgical group three patients were admitted because of recurrent angina, and miscellaneous reasons were found in the remaining patients (pacemaker implantation, near-syncope, congestive heart failure, cerebrovascular accident, arteriography of the leg).

At follow up only one patient in each treatment group was not on medical treatment. The drug regimens were varied; however, 28 (76%) patients in the medical group and 18 (47%) in the surgical group were on antianginal treatment, while 24 (65%) and 31 (82%) respectively were still taking oral anticoagulants.

EMPLOYMENT

Of the 69 patients who were employed before catheterisation, 54 (78%) had resumed work and 29 (42%) were still employed at the time of follow up. In the medical group 83% of the patients returned to work after catheterisation and 53% were still working at follow up. In the surgical group 73% of the patients resumed work after operation and 30% were still working at the time of the survey.

Discussion

The present study shows that excellent long term results were obtained with conventional medical or surgical treatment in patients with single vessel coronary artery stenoses that were technically suitable for percutaneous transluminal coronary angioplasty. This retrospective study was not designed to compare the results of medical and surgical treatment and the populations in both treatment groups clearly have distinct baseline characteristics. It has the potential limitations of all retrospective studies. The patients were catheterised 10–15 years ago and coronary heart disease mortality has declined since then; also medical treatment has changed and new classes of medications, such as calcium antagonists, are now available.

Ten year survival is very high (91%) and the analysis shows that it remains excellent in all subsets. Such survival rates resemble those reported in populations with normal coronary arteriograms.[3-5] These results accord with the currently available data of the Coronary Artery Surgery Study randomised trial for patients with single vessel disease (five year survival 96% in the surgical group and 93% in the medical group).[6] In the Veterans Administration randomised trial of coronary bypass surgery for stable angina the eleven year survival rate in patients with one vessel disease was 70% for the surgical group and 65% for the medical group.[7] The higher survival rate found in the present series might be explained in part by the use of internal mammary artery grafts in most of our surgically treated patients, whereas patients in the Veterans Administration trial had saphenous vein grafts in which long term patency is much lower.[8] The difference in survival of the medically treated groups is difficult to explain: all patients in the Veterans Administration trial but only two thirds in our medical group had angina pectoris at entry to the study; the drug regimen of the patients during follow up was also probably different and most of our patients had received oral anticoagulants, which may be important because coronary artery thrombosis is the main cause of myocardial infarction.[9] Moreover, there is no means of knowing how many of the patients with one vessel disease in the Veterans Administration study or in the Coronary Artery Surgery Study randomised trial had coronary stenoses that were technically suitable for percutaneous transluminal coronary angioplasty.

To our knowledge, only two studies have analysed the outcome in potential cadidates for percutaneous transluminal coronary angioplasty.[10 11] Both, however, have a shorter follow up (four and five years respectively). In the series from Duke University, five year survival is 97% in the medical group and 91% in patients who were treated surgically.[11] In the series of the Coronary Artery Surgery Study, however, the coronary angiograms were not reviewed and factors such as the assessibility of the lesion to the balloon catheter or the presence of calcification were not assessed.

Beside these favourable results in terms of survival, the quality of life of the patients over the ten year follow up period is satisfactory. Although nearly all patients were on medical treatment at follow up, most felt well and few felt worse than at the time of catheterisation. Four (10%) of the medically treated patients had late coronary bypass surgery and an additional 10 (26%) required admission to hospital because of cardiovascular events; there was a similar proportion (10 (26%)) of late hospital admissions for cardiovascular events in the surgical group. These results accord with reported studies of potential percutaneous transluminal coronary angioplasty candidates.[10 11]

Lastly, employment data are also satisfactory, with 54 (78%) of the patients who were employed resuming work after catheterisation or surgery. Similar re-employment rates were found in a recent study of employment after percutaneous transluminal coronary angioplasty in France,[12] and in a report from the National Heart, Lung, and Blood Institute coronary angioplasty registry.[13]

Patients with single vessel disease that could be treated with percutaneous transluminal coronary angioplasty have an excellent long term outcome with standard medical or surgical treatment and it seems doubtful that percutaneous transluminal coronary angioplasty can improve the prognosis of such patients. Percutaneous transluminal coronary angioplasty, however, is likely to improve symptoms as much as surgical treatment and at a lower cost.[14] Similarly, drug requirements should be less after percutaneous transluminal coronary angioplasty than with conventional medical treatment for angina. As a prospective randomised trial of percutaneous transluminal coronary angioplasty and conventional treatment in patients with single vessel disease is now unlikely, retrospective studies, although they are of a more limited scientific value, are the only way in which to compare the long term results of percutaneous transluminal coronary angioplasty. The present study is continuing and should provide information for the evaluation of the current results of percutaneous transluminal coronary angioplasty.

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Percutaneous transluminal coronary angioplasty of one vessel for refractory unstable angina pectoris: efficacy in single and multivessel disease

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SUMMARY Forty patients with unstable angina refractory to medical treatment had one vessel percutaneous transluminal angioplasty to the most stenotic lesion in a major coronary artery. The procedure was successful in 35 patients, and the remaining five patients underwent emergency coronary artery bypass graft surgery. The initial success rate (84%) for the 16 patients with single or the 19 patients with multivessel disease (90%) was similar. At early follow up (average nine days) all patients with successful angioplasty remained symptomatically improved; 10 patients (83%) with single and 10 patients (63%) with multivessel disease had negative treadmill stress tests. Five of six cardiac events occurred within the intermediate (average 11 months) follow up period; two patients had recurrent refractory unstable angina, two had angioplasty for progression of disease in a vessel not previously treated by angioplasty, and one had bypass graft surgery. During late (average 26 months) follow up one patient had a non-fatal myocardial infarction while seven patients (58%) with single vessel disease and nine patients (75%) with multivessel disease had negative stress tests; 29 of 40 patients showed long term improvement.

Unstable angina pectoris can rapidly progress to myocardial infarction or death despite vigorous medical treatment.[1-4] Thus patients with unstable angina are usually admitted to the coronary care unit and treated with multiple drugs including long and short acting nitrates,[5] β blockers,[6] antiplatelet agents,[7] and calcium channel antagonists.[8 9] Despite these measures some patients continue to experience angina and because they are at high risk for myocardial infarction and death[10] they are considered for early coronary artery bypass surgery. Recent investigations have shown that like surgical treatment percutaneous transluminal coronary angioplasty may be effective in the treatment of unstable angina pectoris[11-13] even in emergency situations in patients who do not respond to medical treatment.[14] Most patients in these earlier studies had single vessel coronary artery disease. This is not a common angiographic finding in patients with unstable angina where the majority have multivessel disease.[2] Consequently, the efficacy of percutaneous transluminal coronary angioplasty in patients with unstable angina that is refractory to maximal medical treatment and multivessel disease is not well defined.

We have evaluated the immediate and late symptomatic, functional, and angiographic state of patients after percutaneous transluminal coronary angioplasty of a single, critically stenotic, major artery for refractory unstable angina. Thus this study compares the results of complete angioplastic revascularisation in single vessel disease with those of incomplete angioplastic revascularisation in multivessel disease in patients with refractory unstable angina.

Patients and methods

PATIENTS

During a two year enrolment period 40 patients with refractory unstable angina entered this study. Refractory unstable angina was defined as the persistence of anginal symptoms despite maximally tolerated combined β adrenergic blockade, nitrates, antiplatelet treatment, and/or calcium antagonists

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when given for at least 48 hours.

Unstable refractory angina was subdivided as follows: (*a*) occurring at rest or with minimal effort; (*b*) of recent onset (<1 month and progressively increasing in frequency, duration, and/or severity); (*c*) occurring < six weeks after myocardial infarction.[15] Acute myocardial infarction was ruled out by serial creatine kinase measurements and electrocardiograms obtained over a minimum of 48 hours in the coronary care unit. No patient included in this study had congestive heart failure, cardiomyopathy, valve disease, or left ventricular aneurysm. No attempt was made to negotiate totally occluded vessels, left main lesions, or any lesion greater than 8 mm in length and these patients were excluded from the study.

The details of percutaneous transluminal coronary angioplasty, risks, benefits, and the possibility of emergency coronary artery bypass surgery were explained to each patient. Informed written consent was obtained from the patient and an immediate relative.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY PROCEDURE

Routine coronary angiography was performed by the standard Seldinger technique. The severity of coronary lesions was measured as the maximum percentage diameter narrowing in any standard radiographic view. Percutaneous transluminal coronary angioplasty was performed by the Grüntzig technique[16] modified for use with a steerable system. In patients with one vessel disease, coronary angioplasty was performed if a stenosis of ≥70% was present. In multivessel disease, defined as ≥70% stenosis in two or more coronary arteries, a single percutaneous transluminal coronary angioplasty was performed to the most stenotic lesion within a major vessel. Just before angioplasty, patients received prophylactic sublingual glyceryl trinitrate (0·3 mg) and intravenous heparin (10 000 IU) to prevent possible coronary spasm and thrombosis respectively. Balloon inflations were repeated to produce a satisfactory dilatation as determined by a reduction in the pressure gradient across the lesion and an improvement in angiographic appearance of the stenosis. Multiple projection coronary arteriography was performed to confirm the result. An angioplasty procedure was considered successful when it reduced the stenotic lesion to ≤50% and the transstenotic pressure gradient by ≥30 mm Hg.

For the first 24 hours after angioplasty, patients were monitored in the coronary care unit, where serial electrocardiograms were obtained and serial creatine kinase activity was measured as clinically indicated. For this first 24 hour period after angioplasty, femoral sheaths were left in place and patients were treated with intravenous heparin. Antianginal treatment including intravenous glyceryl trinitrate was given during the initial 24 hours after angioplasty and then gradually tapered off.

FOLLOW UP EVALUATION

Successfully treated patients were followed at regular clinic visits. The severity of angina was graded according to the New York Heart Association classification. Patients were only followed until the following cardiac end points: recurrence of refractory unstable angina; percutaneous transluminal coronary angioplasty of a vessel other than the vessel originally dilated for relief of refractory unstable angina; myocardial infarction; and death. Patients who had percutaneous transluminal angioplasty for restenosis of the originally dilated vessel for other than refractory unstable angina remained in the study.

Treadmill stress tests with the standard Bruce protocol were performed within one month of angioplasty, and at three, six, and every six months after angioplasty. No patient was taking digitalis. All antianginal medications except vasodilators were stopped 24 hours before exercise testing. Vasodilators were withdrawn six hours before the stress test. All 12 standard electrocardiographic leads were monitored throughout the test. A horizontal or downsloping ST segment depression of 0·1 mV or more occurring 0·08 s after the J point during exercise was regarded as a positive test. Because many patients had numerous stress tests, results of the test done within the first 30 days, the most recent within one year, and the most recent done at least one year after angioplasty are reported.

In the event of recurrence of anginal symptoms or a positive treadmill stress test, patients were advised to undergo repeat coronary angiography, and if indicated repeat percutaneous transluminal coronary angioplasty was performed.

TIMING OF FOLLOW UP EXAMINATIONS

Follow up is divided into early (within one month of angioplasty), intermediate (one month to 12 months after angioplasty), and late (> 12 months after angioplasty).

DATA ANALYSIS

Data are expressed, when appropriate, as the mean (1 SD). We use the Statistical Analytical System on an IBM 4381 to test for intragroup significance by a paired *t* test, proportions by either chi-square analysis or the Fisher exact test as appropriate, and morbidity by actuarial analysis. The term significant used within the text implies a p value $< 0{\cdot}05$.

Results

PATIENT CHARACTERISTICS AND CORONARY ANGIOGRAPHIC FINDINGS

There were no significant differences between the characteristics of patients with single or multivessel disease (table 1). In patients with multivessel diseases, 19 had two vessel disease and two had significant disease within all three major coronary vessels.

IMMEDIATE RESULTS OF ANGIOPLASTY

One vessel percutaneous transluminal coronary angioplasty was initially successful in 35 (88%) of 40 patients (table 2). Patients with single or multivessel disease had similar results. The initial success rate for angioplasty of lesions of either the left anterior descending or left circumflex coronary arteries was also similar in patients with single or multivessel disease. The initial success rate was lower in patients who had angioplasty of the right coronary artery and single vessel disease than in patients who had angioplasty of the right coronary artery and multivessel disease, but this difference was not statistically significant ($p > 0.37$). Furthermore, initial success rates for proximal (87%), mid (100%), and distal (83%) lesions were not significantly different. In the 35 successfully treated patients, angioplasty reduced the mean (SD) stenosis from 84 (10)% to 20 (5)% ($p < 0.001$) and the mean (SD) pressure gradient from 60 (18) mm Hg to 12 (11) mm Hg ($p < 0.001$). Angioplasty failed in five patients who went to emergency coronary artery bypass graft surgery: three for impending myocardial infarction caused by vessel occlusion and two patients for recurrent coronary spasm.

EARLY FOLLOW UP (WITHIN ONE MONTH)

Thirty five patients were asymptomatic during the early follow up period and had no cardiac events (fig 1). Antianginal medications were stopped in 14 (40%) before discharge while the remaining 21 patients were discharged while medication was gradually stopped. Eighteen of these 35 patients were hypertensive and nine were discharged on β blockers or calcium channel blockers. Treadmill stress tests were performed by 28 (80%) of 35 patients (table 3). This test was negative in 20 (71%) patients. Within the first month no patient had repeat angiography or angioplasty. Thus all 35 patients entered intermediate follow up.

INTERMEDIATE FOLLOW UP (MEAN 11 MONTHS)

Twenty three (66%) of these 35 patients remained symptom free, seven (20%) had class II angina, and five (14%) had a cardiac event. Figure 1 compares symptoms in patients with single vessel disease and those with multivessel disease. Of the 23 symptom free patients, six were taking no medications while the remaining 17 were taking β blocker calcium channel blockers or both. Eleven of these 17 symptom free patients continued on these antihypertensives while the remaining six normotensive patients were taking small prophylactic doses of β blockers or

Table 1 *Clinical features in 40 patients*

Patient characteristics	*SVD No (%)*	*MVD No (%)*	*Total No (%)*
Patients	19 (48)	21 (52)	40 (100)
Sex (male)	14 (35)	14 (35)	28 (70)
Average age (years (range))	55 (31–82)	56 (43–74)	56 (31–82)
Previous myocardial infarction	2 (5)	6 (15)	8 (20)
Previous CABG	1 (3)	1 (2)	2 (5)
New onset of angina at rest	7 (18)	5 (12)	12 (30)
Crescendo angina	11 (28)	8 (20)	19 (48)
Angina within six weeks of AMI	1 (3)	8 (20)	9 (23)
Diabetes mellitus	1 (3)	4 (10)	5 (13)
Essential hypertension	10 (25)	8 (20)	18 (45)

AMI, acute myocardial infarction, CABG, coronary artery bypass graft, MVD, multivessel disease; SVD, single vessel disease.

Table 2 *Vessel in which percutaneous transluminal coronary angioplasty was attempted and immediate results*

	SVD		*MVD*		*Total*	
	Attempted No	*Successful No (%)*	*Attempted No*	*Successful No (%)*	*Attempted No*	*Successful No (%)*
LAD	14	12 (86)	10	8 (80)	24	20 (83)
LCX	1	1	6	6 (100)	7	7 (100)
RCA	3	2 (67)	5	5 (100)	8	7 (87)
CABG	1	1	0	0	1	1
Total	19	16 (84)	21	19 (90)	40	35 (88)

CABG, coronary artery bypass graft, LAD, left anterior descending, LCX, left circumflex, MVD, multivessel disease, RCA, right coronary artery, SVD, single vessel disease

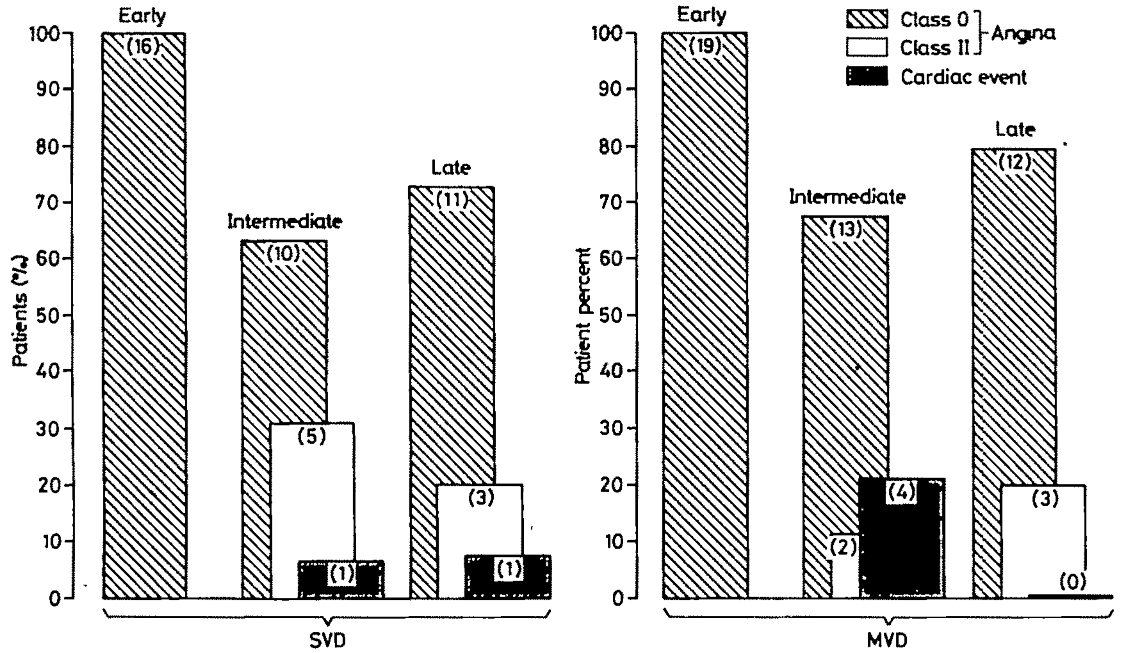

Fig 1 *Early, intermediate, and late follow up after successful one vessel percutaneous transluminal coronary angioplasty in patients with unstable angina pectoris that was refractory to medical treatment. The numbers in parentheses indicate the number of patients. The severity of anginal symptoms is classified according to the New York Heart Association classification. Comparisons between patients with single vessel coronary disease (SVD) and multivessel coronary disease (MVD) did not reach statistical significance.*

calcium channel blockers or both. All seven patients with symptoms were taking β blockers, nitrates, and calcium antagonists. Treadmill stress tests (table 3) were performed by 22 (63%) patients and were negative in 14 (64%).

Within the first 12 months two patients had a recurrence of refractory unstable angina. In both patients angiography showed restenosis of the vessel. This cardiac event constituted a failure of treatment and both patients were excluded from further follow up. There were no deaths and no patient sustained a myocardial infarction during this period. Fourteen patients had repeat coronary angiography for class II or III angina and a positive treadmill stress test. In eight patients a restenosis was seen. Two other patients had progression of disease within a vessel in which angioplasty had not previously been attempted. In the remaining four patients there was no change from the post-angioplasty angiogram. Percutaneous transluminal coronary angioplasty was repeated in six of the eight patients with restenosis and was successful in five. One patient had emergency bypass graft surgery. The two patients with progression of disease within an artery not originally treated by angioplasty for refractory unstable angina had successful angioplasty but were excluded from further follow up. Thus 30 of 35 patients remained in the study at one year.

LATE FOLLOW UP (MEAN 26 MONTHS, RANGE 12 TO 36 MONTHS)

At late follow up in the 30 patients, 23 (77%) were symptom free, six (20%) had symptoms, and one had a non-fatal myocardial infarction. Eight of the 23 symptom free patients were not taking an antianginal agent while 15 were taking β blockers or calcium channel blockers or both. Of these 15, 13 hypertensive patients were continued on β blockers or calcium channel blockers or both while two normotensive patients were given prophylactic doses of these drugs. All six patients with symptoms who were taking nitrates and β blockers and calcium channel blockers had class II angina. The percentage of patients with symptoms was similar in patients with single vessel disease and multivessel disease (fig 1). Treadmill stress tests (table 3) were performed by 24 patients and were negative in 16 (67%). During this late follow up, 12 of the 30 patients had repeat coronary angiography. In three patients, progression of disease was seen within the vessel that had been treated by angioplasty. No patient who had angiography showed progression of disease within a vessel that had not previously been treated by angioplasty. One patient had no change in coronary angiographic anatomy despite chest pain. Percutaneous transluminal coronary angioplasty was successfully repeated in two patients for restenosis, while one

Table 3 *Treadmill stress tests during follow up*

	Early			*Intermediate*			*Late*		
	SVD No (%)	*MVD No (%)*	*Total No (%)*	*SVD No (%)*	*MVD No (%)*	*Total No (%)*	*SVD No (%)*	*MVD No (%)*	*Total No (%)*
Patients	12	16	28	8	14	22	12	12	24
Negative TMST	10 (83)	10 (63)	20 (71)	6 (75)	8 (57)	14 (64)	7 (58)	9 (75)	16 (67)
Positive TMST	2 (17)	6 (37)	8 (29)	2 (25)	6 (43)	8 (36)	5 (42)	3 (25)	8 (33)
Ischaemic changes PTCA area	1 (8)	1 (6)	2 (7)	2 (25)	1 (7)	3 (14)	4 (33)	0	4 (17)
Exercise duration (minutes)	7	6	6	8	6	7	7	8	7
85% PHR	7 (58)	7 (44)	14 (50)	7 (88)	7 (50)	14 (64)	7 (58)	7 (58)	14 (58)

MVD, multivessel disease; PHR, predicted exercise heart rate adjusted for age and sex; PTCA, percutaneous transluminal coronary angioplasty; SVD, single vessel disease; TMST, treadmill stress test.

patient declined repeat angioplasty. Thus 29 (73%) of 40 patients had long term symptomatic improvement (fig 2). After successful angioplasty six (17%) patients had cardiac events; in five these occurred within six months of angioplasty (fig 3).

Discussion

The present study suggests that percutaneous transluminal coronary angioplasty of one vessel may be an alternative to coronary artery bypass graft surgery in patients with unstable angina that is refractory to medical treatment. It also shows that selective coronary angiography may be reliable in identifying lesions precipitating refractory unstable angina in patients with multivessel disease. Coronary artery bypass graft surgery has been the only accepted treatment for these patients. De Feyter *et al* have described the feasibility of percutaneous transluminal coronary angioplasty in this subset of patients as an alternative to coronary artery bypass graft surgery.[14] Their study indicated that percutaneous transluminal coronary angioplasty relieves symptoms, improves exercise capacity, and reduces the frequency of myocardial infarction and death in the first year in patients who generally had single vessel disease. On the other hand, we studied a population in which half the patients had single vessel disease and half had multivessel coronary arterial disease. We followed them for up to three years after angioplasty. Percutaneous transluminal coronary angioplasty was performed as an emergency procedure in the study of De Feyter *et al* but not in ours.

The procedural success rate for the current study is similar to that reported for percutaneous transluminal coronary angioplasty in stable angina[17 18] and higher than the 61–76% success rate reported in earlier studies of patients who generally had single vessel disease and unstable angina.[11-13] The National Heart, Lung, and Blood Institute reported acute myocardial infarction in 9% and in-hospital mortality in 0·9% of patients with unstable angina during percutaneous transluminal coronary angioplasty[11] while in another study the frequency of emergency coronary artery bypass graft surgery was 7% with an in-hospital mortality of 1·7%.[14] The frequency of emergency bypass surgery in the present study was somewhat higher (12%) but with no in-hospital mortality and no significant difference between patients with single or multivessel disease. In the early follow up period all patients with either single or multivessel disease in whom angioplasty was successful became symptom free and improved their exercise capacity. During this period no patient died or sustained myocardial infarction.

Late follow up in our study showed that the proportion of patients with symptomatic improve-

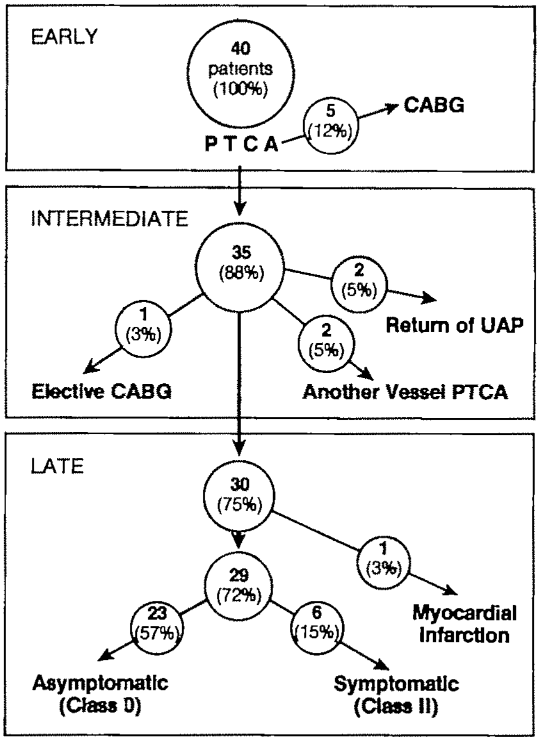

Fig 2 *Diagrammatic representation of the course of patients after one vessel percutaneous angioplasty (PTCA) for the relief of refractory unstable angina (UAP).*
CABG, coronary artery bypass graft surgery.

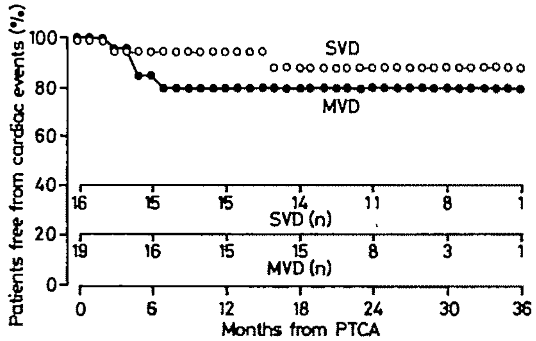

Fig 3 *Comparative actuarial analysis of cardiac events in patients with either single vessel coronary artery disease (SVD) or multivessel coronary artery disease (MVD) who had one vessel percutaneous transluminal coronary angioplasty (PTCA) for the relief of refractory unstable angina. The numbers below the abscissa indicate the number of patients being followed. There was no statistical difference in plots comparing patients with single vessel or multivessel disease.*

ment was the same in the groups with single vessel disease and multivessel disease. These results are similar to those reported in a study of patients with unstable angina and single vessel disease in which successful percutaneous transluminal coronary angioplasty was successful (80%) as bypass surgery in improving symptoms.[11] None the less, although patients with multivessel disease and one vessel percutaneous transluminal coronary angioplasty are asymptomatic they often have a positive treadmill stress test. This may be attributable to incomplete revascularisation. Two groups have attempted to produce complete revascularisation in patients with multivessel disease by percutaneous transluminal coronary angioplasty.[19 20] Knudtson *et al* reported no difference in the clinical course when complete or incomplete revascularisation was achieved by percutaneous transluminal coronary angioplasty in patients with stable angina and multivessel disease.[19] Similarly, anginal patients with multivessel disease had residual ischaemia during exercise with positive treadmill stress tests after angioplasty.[21-24]

Thus our data suggest that percutaneous transluminal coronary angioplasty of a single critically stenosed artery may be a viable alternative to surgical revascularisation and may be associated with fewer cardiac events than other treatments.[2 3 25] This was not a randomised study—randomisation would require a single graft to the most stenotic lesion in patients with multivessel disease rather than complete revascularisation—however, it does compare patients with complete revascularisation (single vessel disease and one vessel angioplasty) and those with incomplete revascularisation (multivessel disease and one vessel angioplasty). The results of incomplete and complete revascularisation are similar.

In patients with unstable angina there is a considerable increase in circulating platelet aggregates,[26 27] platelet factor IV, β thromboglobulin, and thromboxane A_2.[28] These alterations in platelet homoeostasis strongly suggest that platelets are an important faction within the culprit lesion in the precipitation of unstable angina. Smitherman in his review of unstable angina argues that, based on such evidence, the onset of unstable angina reflects a juncture at which thrombotic events rapidly progress at the site of fixed coronary stenosis to produce dynamic coronary stenosis.[29] Such thrombi within the culprit lesion have been visualised with angioscopy.[30] In such a situation anticoagulants may be effective in the management of unstable angina and indeed two large scale multicentre clinical trials have shown that aspirin is effective in treating unstable angina.[7 31]

Yet there are patients who despite taking maximal tolerated medications, including anticoagulants, remain refractory to medical treatment. In that subpopulation percutaneous transluminal coronary angioplasty may, by reducing the fixed coronary stenosis, prevent the development of the local environment necessary for platelet activation. Nevertheless, as angioplasty may produce iatrogenic trauma within the coronary artery heparin or some other anticoagulant should be given for a short time after angioplasty.

Long term anticoagulation was not attempted in this study. Such treatment may reduce the incidence of restenosis but no placebo controlled studies have yet been reported and published reports are uncertain whether long term anticoagulation significantly alters the prognosis after percutaneous transluminal coronary angioplasty.[32]

In conclusion, the results of the current study indicate that one vessel percutaneous transluminal coronary angioplasty will produce the symptomatic relief of refractory unstable angina pectoris with an improvement in exercise tolerance and a low incidence of cardiac events.

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Lack of association between haemostatic variables and the presence or the extent of coronary atherosclerosis

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SUMMARY Blood samples were taken for haemostatic analysis from 225 patients with angina pectoris who were admitted to hospital for coronary angiography. β thromboglobulin, platelet factor 3, platelet factor 4, factor VII:C, factor VIII:C, von Willebrand factor antigen, activated partial thromboplastin time, fibrinogen, antithrombin III, protein C:Ag, plasminogen, and antiplasmin were measured before angiography. Patients who had had a myocardial infarction in the two months before the investigation were excluded from the study. Multiple linear regression analysis showed that none of the haemostatic variables contributed independently to the prediction of an angiographic score that indicated the extent of coronary atherosclerosis. History of myocardial infarction, male sex, worsening of angina pectoris, serum triglycerides, and ejection fraction were independently associated with the angiographic score. There were some significant correlations between haemostatic variables and conventional risk factors for coronary heart disease.

Thus data obtained from haemostatic analyses of peripheral venous blood do not permit the presence or the extent of atherosclerosis in coronary arteries to be predicted.

There is increasing evidence that coronary heart disease is associated with an activation of the clotting system. Coronary thrombosis occurs in most patients with acute myocardial infarction,[1 2] and there is also epidemiological evidence indicating the pathogenetic importance of haemostatic function in coronary heart disease.[3] The precise role of haemostatic factors in the presence of coronary atherosclerosis, however, is still unknown.

Although recent clinical data support the proposition that activation of the coagulation and the platelet system is closely associated with myocardial ischaemia,[4 5] there is little information on the relation between the development of coronary atherosclerosis and the haemostatic system. Nichols *et al* did not detect increased concentrations of platelet factor 4, β thromboglobulin, and fibrinopeptide A in a group of patients with abnormal coronary angiograms without previous myocardial infarction.[6]

We have measured several haemostatic variables in blood samples from 225 patients with angina pectoris. All of them also had coronary angiography within the next two days. We graded the extent of coronary atherosclerosis according to an angiographic score and studied the associations of this score with different clinical variables as well as the haemostatic tests. Thus the aim of this study was to find out, in a cross sectional survey, whether there was a relation between stenotic disease and clotting activity.

Patients and methods

PATIENTS

We studied men and women of all ages with angina

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who were admitted to hospital for coronary angiography. We excluded patients with non-cardiac diseases likely to cause death within one year, right heart failure with peripheral oedema, valve defects, or acute myocardial infarction within the preceding two months. Angina was described as "worsening" if the patient said that the attacks of chest pain had increased in frequency or in severity within recent weeks. Blood was drawn in the morning from patients at rest who had fasted and not smoked for at least eight hours. A record was kept of any drugs, particularly anticoagulants and platelet inhibitors, taken within 10 days before blood sampling.

CORONARY ANGIOGRAPHY

Left ventricular catheterisation and coronary angiography were performed percutaneously from the femoral artery according to the Judkins' technique.[7] Coronary atherosclerosis on the arteriograms was scored from 1 to 5 as (1) no changes, (2) less than 50% stenosis (diameter reduction) in one or more vessels, (3) at least 50% stenosis in one vessel, (4) at least 50% stenosis in two vessels, and (5) at least 50% stenosis in three vessels. The ejection fraction was estimated according to Dodge *et al*[8] as modified by Kennedy *et al*.[9] Akinesia and dyskinesia were defined according to Herman *et al*.[10]

BLOOD SAMPLES

Samples were drawn by venepuncture with a 19 gauge butterfly system by specially trained staff. The first 5 ml was not used for haemostatic analyses. Blood for analysis was collected into precooled tubes containing Thrombotect. (Abbott, North Chicago, USA) reagent (9 + 1 v/v). These blood samples were used for the assays of platelet factor 4 and β thromboglobulin. Blood samples were centrifuged at 0°C for 60 min at 1900 *g*. Plasma was quick frozen and kept at −70°C until assay. Blood for coagulation assays was mixed (9 + 1 v/v) with tri-sodium citrate solution (0·130 mol/l, pH 7·5). Blood was centrifuged for 30 min at 2500 *g* (20°C) within 60 minutes of venepuncture. Plasma was snap frozen and kept at −70°C before analysis. Samples that were used for assays of activated partial thromboplastin time and platelet factor 3 were not frozen and were used immediately.

HAEMOSTATIC ASSAYS

Platelet factor 4 in plasma was measured by the radioimmunoassay kit produced by Abbott and β thromboglobulin by a radioimmunoassay kit supplied by Amersham (Buchler, Braunschweig, West Germany).

Factor VII:C and factor VIII:C were measured by a one-step assays with reagents and factor VII-deficient plasma from Behringwerke AG (Marburg, West Germany). Standard human plasma (Behringwerke) and a plasma pool prepared from 25 male donors (aged 20–40 years) were used as a reference plasma for the standard curves for factor VII:C and factor VIII:C respectively. Results were expressed as percentages of the standards. Fibrinogen was measured according to the method of Clauss,[11] with instructions and reagents from Behringwerke. Platelet factor 3 was measured in freshly prepared platelet rich plasma by a microcoagulation assay described in detail elsewhere.[12]

Activated partial thromboplastin time was measured semiautomatically with a coagulometer (Amelung, Lemgo, West Germany) and a cephalin reagent provided by the National (UK) Reference Laboratory for Anticoagulant Reagents and Control, Manchester. The biological activities of the protease inhibitors antithrombin III and antiplasmin were measured with the synthetic substrates S2238[13] and S2251,[14] respectively, supplied by KabiVitrum (Munich, West Germany). Plasminogen was measured by means of the synthetic substrate S2251[15] supplied by Kabi. von Willebrand factor antigen was measured by the electroimmunoassay described by Laurell.[16] Heterologous antiserum against human von Willebrand factor:Ag (Behringwerke) was used. The results were expressed as a percentage of the standard prepared from normal human blood donors as described above. Protein C antigen was assayed by an enzyme linked immunoadsorbent assay kit[17] (Boehringer Mannheim, Mannheim, West Germany).

STATISTICAL ANALYSIS

Multiple linear regression with forward stepwise selection of variables with a critical p value for entry of 0·05 was applied to test for possible relations between the angiographic score and the other variables. Logarithmic transformation of some variables was used to achieve an approximately normal distribution. p values, given to the nearest significant number if $<0{\cdot}0001$, were derived from the multiple regressions. Independent associations with each of the individual haemostatic variables were also investigated by multiple regression analyses. In analyses of activated partial thromboplastin time, factor VII:C, or protein C:Ag we excluded the 40 patients on anticoagulant treatment. Because the number of comparisons was large results of only borderline statistical significance may have arisen by chance.

Results

CHARACTERISTICS OF THE PATIENTS ADMITTED TO THE STUDY

Two hundred and sixty three patients were admitted to the study. Thirty eight were excluded because angiograms or other relevant documents were lost (n = 12), blood sampling was inadequate (n = 14), or incompatibilities with the entry criteria were detected after entry to the trial (n = 12).

Table 1 summarises the main clinical data of the 225 patients. Ninety nine patients of this group described themselves as ex-smokers and 42 were active smokers. The men were 52·4 (7·1) years old, and the women 52·9 (6·6) (mean (SD)).

INDEPENDENT ASSOCIATIONS WITH THE ANGIOGRAPHIC SCORE

Regression analysis showed that the following were independently associated with increases of the angiographic score: history of myocardial infarction ($p < 0{\cdot}0001$, table 1), male sex ($p < 0{\cdot}0001$, table 1), worsening of angina pectoris ($p < 0{\cdot}0001$, table 1), increased serum triglyceride concentration ($p = 0{\cdot}003$, table 2), and lower ejection fraction ($p = 0{\cdot}02$, table 2). Although white blood cell count (table 2), current or past smoking (table 1), and the presence of akinesia or dyskinesia (table 1) were positively related to the angiographic score, these associations did not remain statistically significant when the above variables had been taken into account. The same applies to serum cholesterol concentrations (table 2), which were positively correlated with serum triglycerides ($r = 0{\cdot}36$). Among those with a past history of myocardial infarction, there was no significant association between the interval since this event and the angiographic score. None of the haematological or haemostatic variables (table 2) contributed independently to the prediction of this score. In addition, no significant differences were seen when the haemostatic variables measured in the patients without angiographic changes were compared with the corresponding values in the patients with coronary atherosclerosis.

INDEPENDENT ASSOCIATIONS WITH HAEMOSTATIC VARIABLES

There were several significant independent associations between haemostatic variables and relevant clinical or laboratory variables. Patients with a history of myocardial infarction had a higher average von Willebrand factor:Ag than those without (123% *vs* 102%, table 2, $p = 0{\cdot}003$). The ejection fraction was associated with concentrations of antiplasmin ($r = 0{\cdot}18$, $p = 0{\cdot}009$) and inversely correlated with concentrations of β thromboglobulin ($r = -0{\cdot}15$, $p = 0{\cdot}03$) and fibrinogen ($r = -0{\cdot}18$, $p = 0{\cdot}006$). Triglyceride concentrations correlated with plasminogen ($r = 0{\cdot}21$, $p = 0{\cdot}003$) and factor VII:C ($r = 0{\cdot}40$, $p = < 0{\cdot}0001$). Increases in cholesterol concentration were associated with higher plasminogen ($r = 0{\cdot}17$, $p = 0{\cdot}02$), antiplasmin ($r = 0{\cdot}22$, $p = 0{\cdot}0009$), and protein C:Ag ($r = 0{\cdot}53$, $p < 0{\cdot}0001$).

Discussion

In the present study we found no associations between the extent of coronary atherosclerosis and an activation of the haemostatic system, either for activation of the platelet and coagulation system or for depression of the fibrinolytic system. These results may seem to be in conflict with recent experimental, angiographic, and histological studies of coronary thrombosis in unstable angina pectoris, acute myocardial infarction, and sudden cardiac death.[1,2,4,5] But none of our patients had an acute myocardial infarction and only a few of them had unstable angina. It is conceivable that myocardial ischaemia is a more important determinant of the activation of the haemostatic system than the extent of anatomical obstruction.[5,18] Earlier studies did not demonstrate a relation between the extent of coronary atherosclerosis and concentrations of platelet

Table 1 *Patient characteristics by angiographic category*

	Angiographic category					
			At least 50% stenosis in.			
Variable	*No changes*	*<50% stenosis*	*One vessel*	*Two vessels*	*Three vessels*	*Overall*
Number of patients	63	14	49	43	56	225
Number of men*	39 (62)	11 (79)	40 (82)	37 (86)	53 (95)	180 (80)
Number with history of myocardial infarction*	12 (19)	2 (14)	24 (49)	30 (70)	38 (68)	106 (47)
Number of current or past smokers*	26 (41)	9 (64)	39 (80)	27 (63)	40 (71)	141 (63)
Number with akinesia or dyskinesia*	2 (3)	0 (0)	18 (37)	21 (49)	21 (38)	62 (28)
Number with worsening of angina*	18 (29)	5 (36)	25 (51)	28 (65)	44 (79)	120 (53)
Mean age (years)†	51 5	51 0	52 2	52 6	54 2	52 5 (7 0)

*Percentages in brackets †SD in brackets.

Table 2 *Mean values of haematological and other variables by angiographic category*

	Angiographic category					
			At least 50% stenosis in.			
Variable	*No changes*	*<50% stenosis*	*One vessel*	*Two vessels*	*Three vessels*	*Overall (SD)*
PVC (%)						
Men	46·7	46·8	46·6	47·8	48·2	47·4 (4·0)
Women	41·3	42·7	43·9	43·8	40·7	42·2 (3·5)
WBC (10^6/ml)*	5·53	6·81	6·16	6·32	6·48	6·12 (1·67)
WBPC (10^6/ml)*	245	259	226	215	232	232 (53)
βTG (ng/ml)*	27·8	31·1	30·8	30·4	30·9	29·9 (11·2)
PF4 (ng/ml)*	3·85	4·44	3·95	3·50	3·53	3·76 (2·46)
vWF:Ag(%)*						
MI	126	105	130	112	128	123 (55)
No MI	109	76	93	103	115	102 (41)
VIII.C (%)*	159	137	155	147	153	153 (76)
ATIII (%)	90	85	88	84	89	88 (13)
Fbg (g/l)*	3·12	3·31	3·28	3·20	3·36	3·24 (0·71)
APTT (s)†	43·2	43·8	43·3	44·0	43·9	43·6 (4·9)
Plg (U/ml)*	4·11	4·10	4·28	4·16	4·34	4·21 (0·75)
α_2 AP (%)	102	106	98	101	100	101 (10)
VII:C (%)*†	123	111	119	118	124	121 (24)
PF3 (%)*	124	119	121	122	121	122 (27)
Protein C (%)†‡	88	86	86	84	91	87 (14)
TG (mg/dl)*	143	159	173	201	192	172 (83)
Chol (mg/dl)*	233	244	257	247	255	247 (48)
EF§	76·6%	80·1%	66·6%	63·0%	63·8%	69·4% (15·2)

*Analysis on log scale. means are geometric and SDs are approximate
†40 patients on anticoagulant treatment were omitted.
‡Protein C results based on a total of 76 patients only.
§Means and approximate SD based on the transformation log (100 − EF).
PCV, packed cell volume, WBC, white blood cells; WBPC, whole blood platelet count; βTG, β thromboglobulin; PF4, platelet factor 4; vWF Ag, von Willebrand factor antigen; MI, patient(s) with previous myocardial infarction; ATIII, antithrombin III, Fbg, fibrinogen; Plg, plasminogen; α_2 AP, antiplasmin, PF3, platelet factor 3, TG, triglycerides, Chol, total cholesterol; EF, ejection fraction.

factor 4[6 19 20] or fibrinopeptide A.[6 21] The last study found that the extent of coronary artery disease and β thromboglobulin concentrations were related in a group of 40 patients.[21] Nichols *et al*, who studied 82 patients with ischaemic heart disease, only saw increased concentrations of platelet factor 4 and β thromboglobulin in those patients in whom myocardial infarction had occurred (more than six months previously, other cases of myocardial infarction being excluded).[6] The results of Nichols *et al*'s study were interpreted as indicating that release of platelet factors in patients with ischaemic heart disease results from the reaction of platelets with the previously infarcted ventricular wall rather than with the arteriosclerotic coronary arteries.

In our study the inverse correlation between lower ejection fractions (which were generally associated with akinesia or dyskinesia of the left ventricle) and β thromboglobulin concentrations, supports this interpretation. The strong positive correlation of antiplasmin and the ejection fraction and the negative correlation of fibrinogen with the ejection fraction that we found have yet to be explained.

We confirmed some other independent associations of haemostatic variables with established risk factors for coronary heart disease. Factor VII:C was strongly related to triglyceride concentration,[3 22] and plasminogen correlated directly with serum concentrations of triglycerides and cholesterol.[23] Protein C:Ag was not raised in our patients (unlike other reports[24]), but it was independently associated with cholesterol. The close relations between factor VII and some components of the fibrinolytic system[25] on the one hand and different indices of hyperlipoproteinemia on the other may well reflect an important pathogenetic factor in coronary heart disease. In contrast, an association between cholesterol or triglyceride concentrations and platelet aggregability could not be confirmed.[26]

The results obtained in the present study do not support the hypothesis that an activation of the haemostatic system associated with atherosclerotic coronary arteries is detectable in venous blood. Rather, they show that correlates of fibrin formation or platelet release are detectable when processes that are secondary to coronary atherosclerosis occur and lead to vessel obstruction and ischaemic injury.

The cross sectional design of the present study means that the question of whether occlusive coronary events are preceded by a long term activation of the haemostatic system remains unresolved. The results of our study do not conflict with previous epidemiological work[3] that suggests that individual clotting factors influence the development of coronary heart disease.

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Automated non-invasive measurement of cardiac output: comparison of electrical bioimpedance and carbon dioxide rebreathing techniques

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SUMMARY Two commercial automated, non-invasive systems for estimation of cardiac output were evaluated. Values of cardiac output obtained by electrical bioimpedance cardiography (BoMed NCCOM3 machine) were compared with values derived from an indirect Fick technique that uses carbon dioxide rebreathing (Gould 9000 IV system) during 103 simultaneous measurements made at rest in 19 randomly selected subjects and on exercise in 11 subjects. Cardiac output values obtained with impedance cardiography were significantly correlated with those measured by the indirect Fick method, although there was a wide scatter with over 73% of the readings lying outside the limits defined by the line of identity ± 20%. This correlation was greatly reduced when stroke volume index was used instead of cardiac output. Indirect Fick results were linearly related to oxygen uptake both at rest and on exercise, while impedance cardiography results did not correlate with oxygen uptake. Impedance cardiography gave consistently lower results for cardiac output than indirect Fick at all levels of exercise. Both machines were easy to use and produced acceptable mean (SE) coefficients of variation (BoMed NCCOM3 7·7 (1·0)%, Gould 9000 IV 10·6 (1·4)%). Further validation is required before either of these machines can be recommended as an alternative to invasive monitoring in clinical practice.

An accurate and reliable non-invasive technique for measuring cardiac output would be of considerable value both in research and in clinical medicine. Over the past 60 years several potentially useful methods have been developed; the most promising of these are electrical bioimpedance cardiography[1-3] and indirect Fick techniques applied to rebreathing of carbon dioxide.[4-6] Use of these methods, however, has been limited by technical problems and uncertainties about their accuracy.[3-6] A high degree of operator skill and experience is needed to perform the tests and to interpret the results accurately.

Recently two fully automated non-invasive cardiac output measurement systems have been developed; each uses a fundamentally different technique. They both use microcomputers to guide the operator, to perform on line data validation, and to analyse the results. They are available commercially and are designed for use in intensive care and coronary care units, in exercise laboratories, and in research.

The aims of this present study were: (*a*) to compare simultaneous cardiac output results obtained both at rest and on exercise with the NCCOM3 (BoMed Medical Manufacturing, Ltd, Irvine, CA), which uses electrical bioimpedance ($\dot{Q}_{EBI}$), and the Gould 9000 IV (Gould Electronics Inc, Dayton, OH), which uses a carbon dioxide Fick method ($\dot{Q}_{Fick}$); (*b*) to compare the results from both of these machines with measured oxygen uptake; and (*c*) to determine the reproducibility, reliability, and ease of use of the machines.

Patients and methods

There were two parts to the study. Firstly, we compared simultaneously recorded supine resting cardiac output measurements obtained with the BoMed NCCOM3 and the Gould 9000 IV in subjects recruited from within the department and from medical outpatient clinics at Flinders Medical

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Centre. In the second study simultaneous measurements were made while normal untrained volunteers performed graded upright cycle exercise.

RESTING STUDY

Nineteen randomly selected subjects agreed to participate in the resting study (15 men and four women aged 18–76 years (mean (SD) 43·5 (16·8)). There were no specific exclusion criteria except unwillingness to participate. Four subjects had essential hypertension requiring drug treatment, and one had controlled cardiac failure, but none had important respiratory disease, thoracic skeletal deformity, or extreme obesity.

Subjects rested for 10 minutes before cardiac output was simultaneously measured by both methods. Three to eight pairs of measurements were taken every five minutes. Great care was taken to ensure that all measurements were taken in strict accordance with the manufacturers' detailed instructions. $\dot{Q}_{Fick}$ was measured by the Gould 9000 IV. Its components are a paramagnetic oxygen analyser, an infrared absorption carbon dioxide analyser, a dry rolling seal spirometer, a microcomputer with a monitor, and a report printer. The analysers have resolutions of 0·01% and accuracies of ±0·10% over the range zero to 25% for oxygen and zero to 10% for carbon dioxide. The spirometer measures expired minute ventilation with a resolution and an accuracy of 0·01 l/min and ±0·025 l/min respectively. The accuracy of these systems has been independently validated.[7] The analysers were calibrated before each study with room air and calibration gas containing 5·17% carbon dioxide in nitrogen. The subject was required to breathe into a one way respiratory valve (Hans Rudolph) attached to a light headframe and connected to the machine via a flexible hose. $\dot{Q}_{Fick}$ was calculated from the Fick equation as follows:

$$\dot{Q}_{Fick} = \frac{\dot{V}CO_2}{C_vCO_2 - C_aCO_2}$$

where $\dot{V}CO_2$ is the rate of carbon dioxide production and C_v and C_aCO_2 are mixed venous and arterial carbon dioxide concentrations. Carbon dioxide production was calculated by continuous analysis of the carbon dioxide concentration and the volume of expired air. Oxygen uptake was similarly calculated. C_aCO_2 was calculated by the computer from the end tidal partial pressure of carbon dioxide from standard dissociation curves. C_vCO_2 was calculated in a similar manner from the partial pressure of carbon dioxide determined by a rebreathing method as described by Collier.[8] This assumes that during rebreathing of a mixture of carbon dioxide in oxygen the concentration of carbon dioxide in the bag, alveoli, and pulmonary capillaries will reach an equilibrium at which time there will be no net exchange across the alveolar capillary membrane. The concentration of carbon dioxide at that point will be equal to that of mixed venous blood. Subjects were required to rebreathe 1·5 times their tidal volume of a mixture of 10% carbon dioxide in oxygen for approximately 15 seconds. The plateau phase which indicated equilibrium was determined by the computer which also performed all calculations and made corrections for temperature and barometric pressure. During rebreathing the output of the carbon dioxide analyser was continuously displayed on a television screen, enabling the operator to confirm that an adequate plateau was achieved.

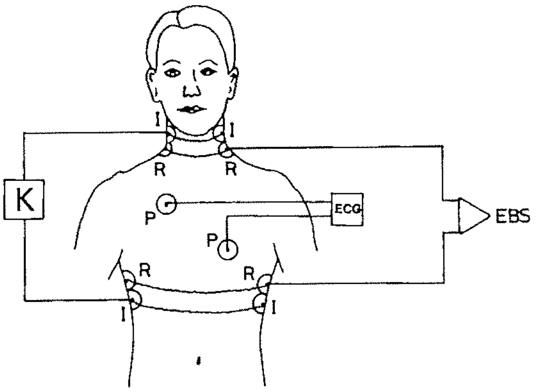

Fig 1 *Electrode positions for measuring the electrical bioimpedance signal (EBS). Pairs of recording electrodes (R) were placed at the root of the neck and at the level of the xiphisternum. The constant current sinusoidal field generator (K) was connected to the injecting electrodes (I) placed 5 cm above and below the recording electrodes. The electrocardiogram (ECG) was recorded using precordial electrodes (P).*

$\dot{Q}_{EBI}$ was measured by the BoMed NCCOM3. The technique depends upon the conversion of changes in thoracic impedance during each cardiac cycle into information about blood flow. Ten, low contact impedance, self adhesive electrodes were positioned for recording the electrocardiogram and bioimpedance signals as shown in fig 1. The machine generated a constant current, high frequency, sinusoidal field across the thorax through the outer pairs of electrodes. An impedance signal was recorded from the inner pairs. Stroke volume (SV) was calculated in ml according to an empirical formula described by Sramek *et al*[9]:

$$SV = VEPT \times T \times \frac{(dz/dt)max}{Zo}$$

where VEPT is the volume of electrically participating tissue (ml), T is the ventricular ejection time (s), Zo is the thoracic base impedance (Ω) and (dz/dt)max is the maximum rate of change of impedance during the systolic upstroke (Ω/s). The VEPT was calculated from the subject's age, sex, and height by a nomogram.[10] Analysis of the impedance signal and calculations were performed on line by the machine, which can give beat by beat or period mean values for $\dot{Q}_{EBI}$, heart rate, and stroke volume.

EXERCISE STUDY

Eleven (nine men, two women; aged 18–39, mean (SD) 28 (4)) of the subjects who took part in the resting study went on to complete the exercise study. None had important cardiovascular or pulmonary disease, thoracic skeletal deformity, or extreme obesity. None of them engaged in regular physical training.

Submaximal upright exercise was performed on a cycle ergometer. For the men, simultaneous measurements of $\dot{Q}_{EBI}$ and $\dot{Q}_{Fick}$ were made at rest while they were seated on the bicycle, after 5 and 10 minutes of exercise at 65 W (400 kpm/min) and after 5 minutes at 130 W (800 kpm/min). Measurements were made at similar times in women but workloads were reduced by 25%.

CALCULATIONS AND STATISTICAL ANALYSIS

Stroke volume index (SVI) was calculated according to the formula:

$$SVI = \frac{\text{Cardiac output}}{\text{Heart rate} \times \text{Body surface area}} (\text{ml/beat/m}^2)$$

Correlation between paired data sets was determined by linear regression analysis. Statistical significance of differences between groups was calculated by standard methods of analysis of variance. Results were expressed as mean (SE). Statistical significance was assumed when $p < 0.05$.

Results

Figure 2 is a scattergram which shows a total of 103 pairs of simultaneous measurements obtained during both the resting and the exercise studies. Although there was a significant correlation ($r = 0.56$, $p < 0.001$), there was a wide scatter with over 73% of the readings lying outside limits defined by the line of identity ±20%. Statistical significance was greatly reduced ($r = 0.24$, $p < 0.05$) when stroke volume index was used instead of cardiac output (fig 3). $\dot{Q}_{EBI}$ was consistently lower than $\dot{Q}_{Fick}$ during all stages of exercise (fig. 4).

Figure 5 shows the relation between cardiac output

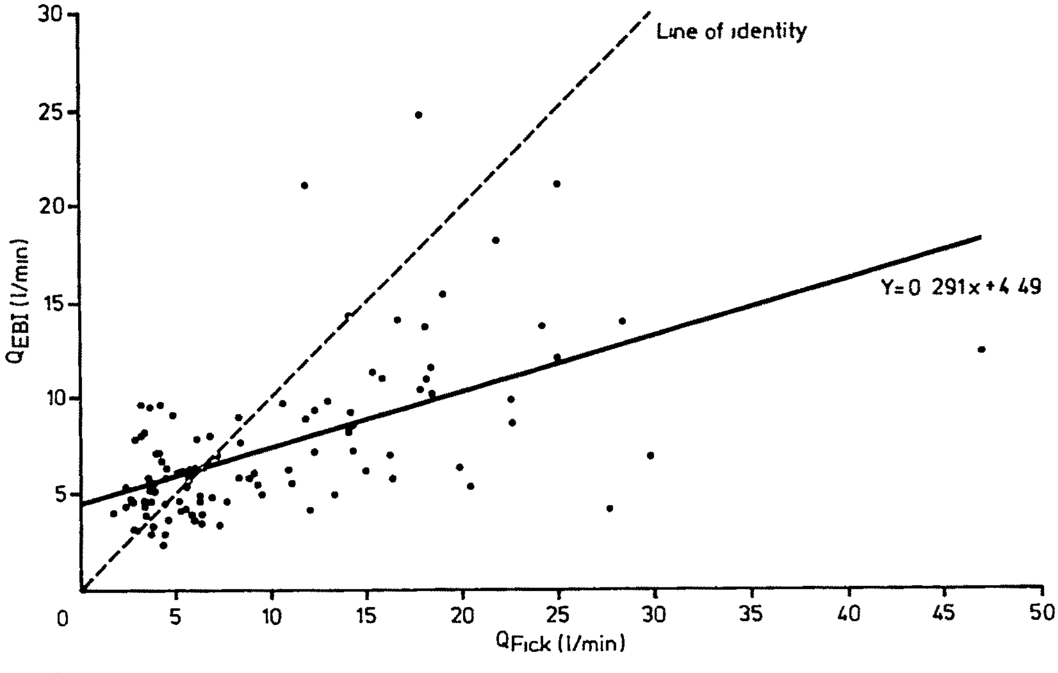

Fig 2 *Scattergram showing 103 paired measurements of cardiac output made at rest and on exercise by electrical bioimpedance ($\dot{Q}_{EBI}$) and carbon dioxide rebreathing indirect Fick ($\dot{Q}_{Fick}$) techniques.*

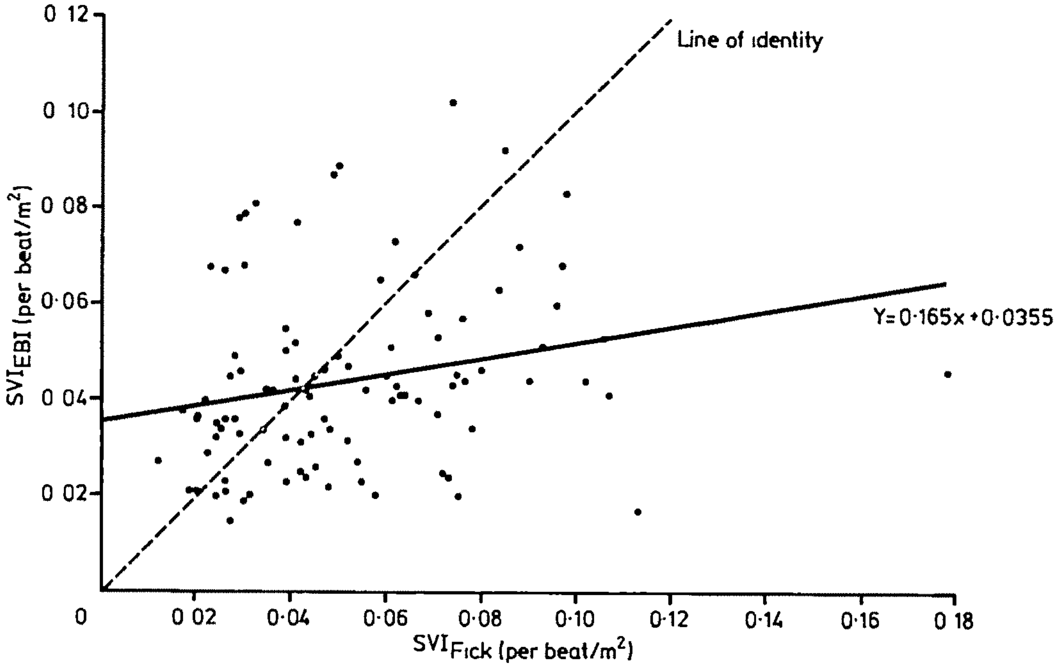

Fig 3 *Scattergram showing comparison between stroke volume index measured by electrical bioimpedance (SVI_{EBI}) and carbon dioxide rebreathing indirect Fick (SVI_{Fick}) techniques. These data were calculated from the points used in fig 2.*

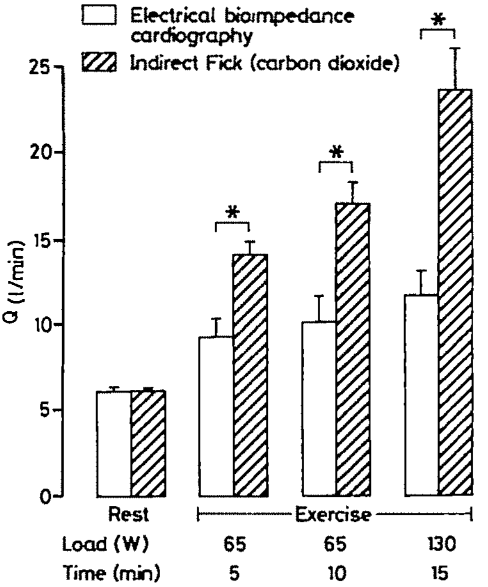

Fig 4 *Cardiac output ($\dot{Q}$) measurments obtained by each machine during graded bycycle exercise in 11 normal volunteers.* * = $p < 0.005$.

and oxygen uptake at rest and during exercise. $\dot{Q}_{EBI}$ was not significantly correlated with oxygen uptake at rest, and only weakly correlated on exercise. $\dot{Q}_{Fick}$ correlated well with oxygen uptake both at rest and on exercise; however, the regression slopes were steeper than previously reported.[11-13]

Coefficients of variation were calculated for the resting data to access random error. The mean (SE) coefficient of variation for $\dot{Q}_{EBI}$ was 7·7 (1·0%) (range of 0–18·2%). Corresponding figures for $\dot{Q}_{Fick}$ were 10·6 (1·4%) (0–21 7%). We found both machines reasonably easy to use. The Bomed NCCOM3 was simply plugged into a power source, switched on, and connected to correctly positioned electrodes. A value related to the volume of electrically participating tissue, determined from a nomogram and the patient's sex, height, and weight, was entered on a keyboard. The machine then produced consecutive real time readings displayed either as beat by beat values or period means.

The Gould 9000 IV was more difficult to operate. The machine had to be switched on for at least an hour to allow temperature stabilisation and had to be calibrated before each study. The operator was required to prompt the computer and to switch in the

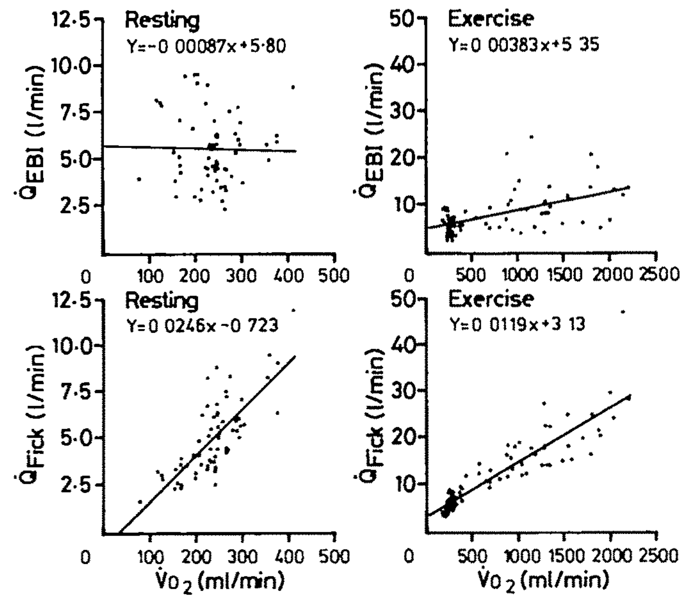

Fig 5 *Scattergrams showing the relation between cardiac output measured by electrical bioimpedance ($\dot{Q}_{EBI}$) and carbon dioxide rebreathing indirect Fick ($\dot{Q}_{Fick}$) techniques and oxygen uptake ($\dot{V}O_2$) both at rest and on exercise.*

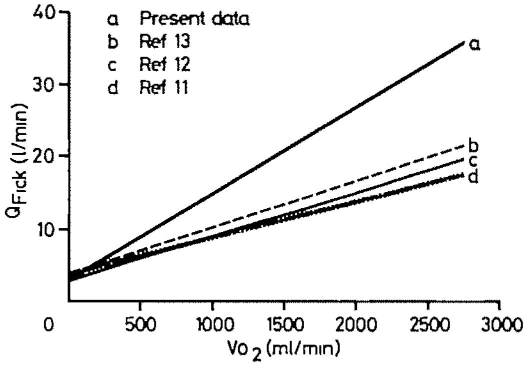

Fig 6 *The regression slope relating cardiac output ($\dot{Q}_{Fick}$) determined by the carbon dioxide rebreathing indirect Fick technique to oxygen intake ($\dot{V}O_2$) in this study (a) was steeper than described by others who used invasive techniques.*

rebreathing mixture in order to obtain individual measurements. None the less, the computer software guides the operator through the calibration and rebreathing procedures. New operators needed about four hours training to use the machine correctly. The technique could only be used in spontaneously breathing subjects.

Discussion

Scientific evaluation of techniques for measuring cardiac output is difficult because there are no gold standards. All available methods, including direct Fick, indicator dilution, radiopharmaceutical, echocardiographic, and Doppler techniques, produce errors of at least ± 10%.[14 15] We chose to use measured oxygen uptake as the standard by which to determine accuracy because many workers have demonstrated that cardiac output is linearly and predictably related to oxygen uptake in normal subjects.[11-15]Many previous studies have evaluated these non-invasive methods. Indirect carbon dioxide Fick methods have been compared with direct oxygen Fick[16] and with indicator dilution[17] techniques, both at rest[18] and on exercise.[17] Studies have been performed in controls[16] and in patients with heart failure[19] and respiratory disease.[20] Most of these studies found that the technique was accurate and reproducible. There have been more than 50 studies to compare electrical bioimpedance cardiography with other methods; most of these have shown good correlations[21-23] though some have found it inaccurate.[24 25]

Published information about the BoMed NCCOM3 and the Gould 9000 IV is scanty, however, despite the fact that they are available commercially. We are not aware of any previous reports validating cardiac output assessment by the Gould 9000 IV and there have been only two papers describing use of the BoMed NCCOM3 in man.[26 27] These groups both found a reasonably good correlation with thermodilution methods in critically ill patients. In one study the analogue first derivative impedance signal was recorded and examined to ensure adequate quality before results were included.[26] This facility is not routinely available with the commercially produced machine. Neither study was able to examine the accuracy of the BoMed NCCOM3 on exercise. This lack of information is particularly disturbing because this machine uses a new and relatively untested stroke volume formula.

$\dot{Q}_{Fick}$ was linearly related to oxygen uptake. The regression slope was steeper than that described before with invasive methods,[11-13] suggesting that the Gould machine may overestimate cardiac output during moderate exercise. An alternative explanation could be that our subjects were untrained and many were older than those who took part in previous studies: these factors may alter the relation between cardiac output and oxygen uptake.[11] In contrast, there was no significant relation between $\dot{Q}_{EBI}$ and oxygen uptake. These data suggest that the carbon dioxide Fick method produced results that were, at least, related to cardiac output, while results derived from electrical bioimpedance cardiography were likely to be wrong. We realise that carbon dioxide production, which was used in the Fick equation, and oxygen uptake were not completely independent variables as they were both calculated from the same minute volume which was measured by the Gould 9000 IV. None the less, oxygen and carbon dioxide were measured by completely independent analysers. Any errors in the measurement of minute volume would equally affect both $\dot{Q}_{Fick}$ and oxygen uptake.

We found a statistically significant correlation between simultaneous measurements of $\dot{Q}_{EBI}$ and $\dot{Q}_{Fick}$, although there was poor agreement for individual measurements. This correlation was greatly attenuated when stroke volume index results from each of the machines were compared. This accords with a previous study that examined electrical impedance cardiography and found that it "did not determine reliably absolute values of stroke index and is not suitable to evaluate changes in stroke index".[3] Other workers found that impedance estimates of an angiographically determined left ventricular stroke volume of 100 ml ranged from 40 to 150 ml.[28] Most reports of the evaluation of electrical bioimpedance cardiography have concentrated on cardiac output rather than stroke volume index. These workers may have produced fortuitous correlations that were not necessarily related to putative electrical impedance changes in the thorax. The empirical formulas used in electrical bioimpedance cardiography were designed to determine stroke volume. Cardiac output is, of course, the product of stroke volume and heart rate, with heart rate being the most important of these determinants, particularly on exercise.[29] Multiplication of electrical bioimpedance-derived stroke volume by independently measured heart rate will be likely to produce correlation when the result is compared with some other measure of cardiac output. In addition, stroke volume is related to the body size. Both the earlier Kubicek formula[1] and the Sramek formula[9] used in the BoMed NCCOM3 use a measure related to body size in the numerator and the thoracic base impedance, which is inversely related to body size,[30] in the denominator. These factors may be in the first or second power depending upon the formula used: both combine to produce stroke volume results that are positively related to body size. Any critical analysis of electrical bioimpedance cardiography should remove the effects of heart rate and body size by examining stroke volume index.

In a neglected paper Hill *et al* examined the principles of electrical bioimpedance in a series of careful in vitro experiments.[31] They found that as a function of blood flow true impedance signals were so small as to be unmeasurable and that impedance cardiographs produced "totally uncalibratable strain gauge type signals". They concluded that "electrical impedance cardiography, as it is currently used and interpreted, appears to be in error". We have found no evidence in published reports or in our data to contradict this statement.

The impedance equipment (BoMed NCCOM3) did not accurately assess cardiac output during exercise although it is recommended for use during diagnostic exercise testing by the manufacturers. Previous studies have shown electrical bioimpedance cardiography to be applicable during exercise.[32 33] We assume that the impedance signals became distorted during exercise, making measurement of the thoracic base impedance, the maximum rate of change of impedance during the systolic upstroke, and the ventricular ejection time inaccurate. Nevertheless, the machine produced readings throughout the test in all subjects. We were unable to find any independent published data on the accuracy and resolution of measurement of these variables by this machine.

We conclude that the Gould 9000 IV carbon dioxide Fick system was reasonably easy to use, produced acceptably reproducible results and was accurate, when compared with measured oxygen uptake, both at rest and on exercise. Further work is required to compare this machine with invasive measurements of cardiac output before it can be recommended for clinical use. The BoMed NCCOM3 electrical bioimpedance cardiograph was very simple to use and gave remarkably reproducible results. Its accuracy compared with oxygen uptake was poor even at rest. The machine was of no value during upright bicycle exercise and of limited value in resting patients. It should not be used in clinical practice as an alternative to invasive monitoring.

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Feasibility and variability of six methods for the echocardiographic and Doppler determination of cardiac output

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SUMMARY The feasibility and the intrinsic variability of six different methods of echocardiographic and Doppler flow determination of cardiac output were analysed in 34 healthy volunteers. Four were excluded because of poor quality echocardiograms. The mean (range) age of the remaining 30 (12 women, 18 men) was 21 years (13–36 years). Cardiac output was calculated by six methods as a product of echocardiographically determined cross sectional area of the aorta (apical and suprasternal views), pulmonary trunk, tricuspid annulus, and mitral annulus (circular and corrected for diastolic variations), and the flow velocity integral measured by Doppler. Cardiac output ranged from 2·79 to 6·56 l/min (4·45 (1·29) l/min) (mean (SD)). The feasibility of the methods ranged from 87% (26 patients) for the aorta from the suprasternal notch to 100% (30 patients) for the mitral orifice corrected for diastolic variations and for the tricuspid valve. The corresponding results for all 34 individuals were 76% and 88% respectively. Three way analysis of variance was performed in the 23 healthy volunteers in whom all six methods were feasible. Interobserver and intraobserver interpretative variabilities were 6·8% and 5·9% respectively. The intrinsic variability of each single measurement of cardiac output, independently of the observer and the method used, was 25%.

Provided the image was suitable for analysis echocardiographic and Doppler flow determination of cardiac output was feasible in most healthy volunteers. But there was significant intrinsic variability for each of different methods. A single value of cardiac output in an individual should be interpreted with caution.

Studies on the echocardiographic and Doppler flow determination of cardiac output mainly consider the validation of the methods against invasive measurements.[1–17] At present there is little information on the feasibility of such methods in clinical settings and on the variability associated with each method.[18–23] We have analysed the feasibility and the intrinsic variability of the results of six different methods of calculating cardiac output in healthy volunteers.

Patients and methods

We studied 34 healthy volunteers. Four were excluded because of poor quality echocardiograms. The mean (range) age of the remaining 30 (12 women, 18 men) was 21 years (13–36 years).

Echocardiograms and pulsed Doppler recordings were made on a Honeywell Ultra-imager with a 3 5 MHz mechanical transducer. Doppler sampled cardiac output (CO) was calculated by six different methods as a product of echocardiographically determined cross sectional area (A) of the aorta,[5 12] pulmonary trunk,[4] mitral annulus[1 12] and tricuspid annulus,[11] and the flow velocity integral over the cardiac cycle (V) measured by Doppler, by the formula CO = (A × V × 60)/cos ϑ. For the purpose

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of the study the cos ϑ was assumed to be 1 for all calculations.[21]

We used two different methods to calculate both the aortic and the mitral flow. The aortic flow curve was recorded from the apex[12] and from the suprasternal notch.[5] The mitral valve flow was calculated by the circular annulus method[12] and the mitral orifice method with correction for diastolic variations.[1]

Still frames of the cross sectional images, derived M mode tracings, and Doppler velocity outputs were recorded on hard copy for three separate cardiac cycles for further analysis. The paper speed for M mode tracings and Doppler velocity outputs was 50 mm/s. Beat to beat variability was not taken into account in this study and each cross sectional, M mode, and Doppler measurement was the mean of the three cycles.

One investigator obtained all the echocardiographic images and Doppler recordings from resting and haemodynamically stable individuals. Established methods were used to achieve the best Doppler signal.[1 4 5 11 12]

Two observers independently and blindly made all the measurements on two occasions. Because of the design of our computer system digitising pad, we had to trace the Doppler flow curves of the three cycles on to a plastic transparency from the hard copy. The traces were digitised independently and blindly by a third observer.[21] The densest part of the velocity trace was taken as the modal velocity. The computer system calculated the area under each curve to determine the mean velocity of flow for each cycle.

The aortic diameter (from inner wall to inner wall) was measured at the onset of the QRS complex from the cross sectional parasternal long axis images, immediately distal to the aortic sinuses.[5] To improve the accuracy, measurements were made on the cross sectional derived M mode recordings for three separate cardiac cycles. The aortic diameter, assumed to be constant throughout systole, was used to calculate the cross sectional area of the aorta.[5]

Doppler flow velocity of the aorta was recorded both from the apex by the method of Lewis *et al*,[12] and from the suprasternal notch by the method of Gardin *et al*.[5] For both methods we tried to place the sample volume immediately distal to the aortic sinuses, where the aortic diameter was measured.

The cross sectional area of the pulmonary artery, which was assumed to be constant throughout systole, was calculated from measurements of maximal systolic diameter.[4] We followed the recommendations of Goldberg *et al*[24] and measured maximum systolic diameter for three separate cardiac cycles from the midwall points. Pulmonary flow curves were recorded by established methods.[4 11]

The cross sectional area of the mitral valve was measured by assuming that the mitral annulus was circular and of a constant cross sectional area throughout diastole, as indicated by Lewis *et al*.[12] For Doppler recordings the sample volume was placed at the level of the mitral annulus as suggested by Lewis *et al*.[12]

For the mitral flow calculation we also used the mitral orifice method with correction for diastolic variations described by Fisher *et al*,[1] and reported elsewhere.[21] Measurement of tricuspid cross sectional area assumed that the tricuspid annulus was circular and constant throughout diastole, as described by Loeber *et al*.[11] The Doppler sample volume was placed just beyond the tips of the tricuspid leaflets.[11]

Final results of cardiac output values are given as the mean of the four measurements obtained by the two observers for all six methods.

STATISTICAL ANALYSIS

We analysed the results for 23 individuals in whom all six methods could be performed. We used a complete 23 × 6 × 2 (subjects × methods × observers) factorial model with repeated measures.[25] The factorial component of "methods" is fixed while "subjects" and "observers" are random factors. In this model the variability was regarded as coming from population, methods, observers (interobserver variability), interactions of these factors, and by repetition of measurements (intraobserver variability). Results were analysed by three way analysis of variance.[25] Unbiased estimates of all the components of variance were obtained as linear combinations of the mean squares in the analysis of variance.[25] The null hypothesis that the contribution of any component is zero was tested by the Fisher F test for variance. To evaluate different factors of interpretative variability for each method of calculating cardiac output, a two way analysis of variance was also performed on the random factors—subjects and observers.[25] Variability was given as absolute values (standard deviation of the corresponding component of variance) and as percentage of the mean.

Results

Calculated Doppler cardiac output values ranged from 2·79 to 6·56 l/min (mean (SD) 4·45 (1·29) l/min). Mean (SD) values were different for each method, ranging from 3 2 (0·6) l/min for the mitral orifice method corrected for diastolic variations to 5·3 (1·3) l/min for the tricuspid annulus method (table 1).

In the 30 individuals who had good quality echocardiograms the feasibility of each method was 97% for the aorta from the apex, 87% for the aorta from the suprasternal notch, 90% for the pulmonary

Table 1 *Cardiac output values of the six different methods*

	Aorta apex	*Aorta suprasternal*	*Pulmonary trunk*	*Mitral annulus*	*Tricuspid annulus*	*Mitral corrected*
No	29	26	27	29	30	30
Mean (l/min)	4·7	4·3	5·0	4·3	5·3	3·2
1 SD (l/min)	1·2	1·1	1·1	1·2	1·3	0·6

trunk, 97% for the circular mitral annulus method, 100% for the mitral orifice method corrected for diastolic variations, 100% for the tricuspid valve. For the total study group of 34 individuals the corresponding results were reduced to 85%, 76%, 79%, 85%, 88%, and 88%.

The interobserver and intraobserver variabilities for cardiac output were 0·305 l/min (6·8%) and 0·265 l/min (5·9%) respectively (table 2). Population variability was 18·3%, and method variability was 16·0% (table 2). Table 2 also shows the variability caused by the interaction between methods and population (18·9%), between observers and population (3·4%), between observers and methods (5·4%), and between observers, methods, and population (4·8%). These results show that there was variation of the methods for different individuals, for the same observer in different subjects, for observers using different methods, and for observers in combinations with methods and subjects. The total interpretative variability of the method was 9·6%—that is the variability caused by observers, repetition of measurements, and the interaction between observers and population. The intrinsic variability of each single measurement of cardiac output, independently of the observer and of the method used, was 25% (total variability without population variability).

Table 2 *Results of three way analysis of variance*

		1 SD (l/min)	*%*
(*a*)	Population	0·825	18·3
(*b*)	Methods	0·723	16·0
(*c*)	Interobserver	0·305	6·8
(*d*)	Methods/population	0·855	18·9
(*e*)	Observer/population	0·153	3·4
(*f*)	Observer/methods	0·245	5·4
(*g*)	Observer/methods/population	0·216	4·8
(*h*)	Intraobserver	0·265	5·9
(*i*)	Total interpretative variability	0·432	9·6
(*j*)	Intrinsic variability of a single measurement	1·120	25·0

d, *e*, *f*, *g*, interactions between factors; *i*, total interpretative variability. variability due to observers, repetition of measurements, and the interaction between observers and population, *j*, intrinsic variability of a single measurement—total variability without variability due to the population
All variability results are statistically significant ($p < 0·01$) (Fisher F test for variance)

Table 3 shows the interpretative components of variability for each method of measuring cardiac output and table 4 shows the interpretative variability due to Doppler tracings and measurement of cross sectional area.

Discussion

We studied the feasibility of six different methods for echocardiographic and Doppler flow determination of cardiac output. Although the subjects of our study were clinically normal, image studies were unsatisfactory in four (12%) of them. We found the same percentage in a separate different earlier series.[21] We also found that, provided the image was suitable for analysis, the six methods were feasible in most individuals.

We analysed the variability of interpretation of the recorded data not the variability due to the recording procedure. Interobserver and intraobserver variabilities were 6·8% and 5·9% respectively. These values are similar to those of an earlier study.[21] There was considerable variability (16·0%) when different methods were used, which was close to the variability due to the population (18·3%). Variability caused by interaction between methods and population was even higher (18·9%), indicating that the results of the methods varied in different individuals.

It is difficult to define the factors that influence such variability. It could be that the reliability of measuring data varies in different subjects with different methods. This will make it very difficult to forecast which method will give the most reliable measurements in any one individual. Furthermore, several factors may be responsible for the discrepancies of each method.

We measured the cross sectional area of the aorta in the parasternal long axis view for both methods. For both methods we tried to place the sample volume immediately distal to the aortic sinuses, where the aortic diameter was measured. Though we tried to follow the procedure described by Gardin *et al* [5] for measurements from the suprasternal notch, in some subjects the position of the sample volume may not have coincided with the site at which the aortic diameter was measured.

Lewis *et al* placed the sample volume in the middle of the left ventricular outflow tract, immediately

Table 3 *Results of two way analysis of variance for each of the six different methods of measuring cardiac output. Variability is given as a percentage*

	Aorta apex	*Aorta suprasternal*	*Pulmonary trunk*	*Mitral annulus*	*Tricuspid annulus*	*Mitral corrected*
Interobserver	2·5*	4·7*	5·6*	16·0*	8·6*	0·1
Intraobserver	6·9	5·8	4·3	6·8	5·5	5·3
Total interpretative variability	7·4	7·8	7·9	20·0	12·0	7·7

*p < 0·01 (Fisher F test for variance).

Table 4 *Results of two way analysis of variance attributable to the interpretation of Doppler measurements and cross sectional measurements for each of the six different methods. Variability is given as a percentage*

	Aorta apex	*Aorta suprasternal*	*Pulmonary trunk*	*Mitral annulus*	*Tricuspid annulus*	*Mitral corrected*
Doppler variability	5·4	7·3†	4·2	7·8	9·2*	10·0*
Cross sectional variability	4·6	4·6	5·4*	13·8†	7·2	7·9

*p < 0·05, † p < 0·01 (Fisher F test for variance for differences between Doppler and cross sectional variabilities).

proximal to the leaflet of the aortic valve.[12] They calculated the area of the aortic annulus from the annular diameter measured immediately proximal to the points of insertion of the aortic leaflets from the parasternal long axis plane.[12] We modified this approach to increase the success rate with all six methods. Though we tried to optimise the Doppler signals, it may be that in some cases we did not achieve alignment with the aortic flow above the aortic sinuses from the apex.

The fact that we measured the aortic diameter from the left sternal edge and velocities from the apex and from the suprasternal notch may also have caused difficulties.

We used the method of Goldberg *et al* to measure the diameter of the pulmonary artery from the midwall points, because of parallel resolution[24]; others prefer to measure the inner diameter.[4]

In calculating the mitral and tricuspid orifices[12 11] we assumed that they were circular with a constant cross sectional area throughout diastole. This may not be true of both valves.

The mitral orifice method, described by Fisher *et al*,[1] implies a correction for diastolic variation, but it seems to give lower values than the other methods (table 1).

We tried to get consistently good quality recordings to avoid one source of variability. We previously observed that the quality of the echocardiograms does not increase variability to an important extent, provided the image is suitable for analysis.[21] Furthermore, the influence of the observer was within clinically acceptable limits (table 2). Further selection of images and tracing may reduce the feasibility of each method to unacceptable levels in clinical practice.

The intrinsic variability of a single given value of cardiac output independent of the observer and method used was ±25%. The mitral and the tricuspid annulus methods gave the greatest variability (table 3). This is consistent with reported data.[20] Whether or not similar reproducibility would be obtained in low or high output states (that is outside the range of values considered in this study) or by using more than three beats for all calculations has yet to be determined. In this paper we examined the suggestion that variability within and between interpreters and between different methods can significantly influence the accuracy of the measurements.[19 20 26 27] We found that in a small group of normal individuals the interobserver and intraobserver variability of analysing the echocardiographic and Doppler measurements required for cardiac output calculations was within clinically acceptable limits. We also found that the echocardiographic and Doppler flow determination of cardiac output was feasible in most healthy volunteers, provided that the image was suitable for analysis.

Nevertheless, the intrinsic variability of different methods was significant and a single value for an individual cannot be entirely reliable.

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Correction of left ventricular asynchrony by coronary artery surgery

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SUMMARY To investigate the effect of coronary artery bypass grafting on the timing of regional left ventricular wall motion, contrast left ventriculograms from 27 patients were digitised frame by frame before and after operation. End diastolic and end systolic volumes, ejection fraction, and peak ejection and filling rates showed no significant change. The commonest preoperative abnormality was delayed onset of inward wall motion during ejection, which was present in 14 patients over 10% (range 5–40%) of the cavity outline, leading to a pattern of "diagonal contours". After operation this pattern had resolved completely in 12 patients and partially in two. Minor abnormalities appeared postoperatively in five but overall the mean (1SD) area affected was reduced by 5 (8)%. The time span between the onset of inward motion in different regions of the cavity also fell significantly after surgery from 190 (50) to 130 (50) ms. Regional hypokinesis (6 cases) and abnormal wall motion during isovolumic contraction (4 cases) or isovolumic relaxation (5 cases) were not consistently affected.

Thus successful coronary artery surgery is without consistent effect on overall left ventricular function, overall hypokinesis, or abnormal wall motion during the isovolumic periods. It does, however, strikingly reduce the asynchrony of wall motion during ejection, suggesting that before operation this abnormality may directly reflect impaired coronary blood flow. The results emphasise the potential value of analysing regional wall motion to elucidate functional abnormalities associated with coronary artery disease.

It is well established that coronary artery bypass grafting is associated with an increase in exercise tolerance in patients limited by angina of effort. Whether this improvement is accompanied by a corresponding change in resting left ventricular function is less clear. Although early results suggested an increase in ejection fraction,[1] these findings have not been confirmed, and it is now generally accepted that basal measurements of overall function are not modified by operation in any clinically significant way.[2] There is, however, little information about possible effects of surgery on the asynchronous wall motion so frequently present in patients with coronary artery disease.

It has been shown that wall motion abnormalities during pacing induced angina consistently arise in segments showing a characteristic pattern of asynchrony at rest.[3] The possibility that this asynchrony at rest might be reversed by restoring normal coronary flow is clearly of potential clinical interest. The present study was therefore undertaken to investigate the effects of bypass grafting on the timing of regional left ventricular wall motion in a group of patients in whom revascularisation had been successful.

Patients and methods

We studied 27 patients (mean (SD) age 52 (7·4) years; 25 men) who had had coronary artery bypass grafting with saphenous vein or internal mammary artery at Harefield Hospital. The patients were selected only in so far as they had all undergone a preoperative and a routine postoperative study and had right anterior oblique angiograms performed on these two occasions that were technically suitable for analysis. Eight had had a myocardial infarction before the first arteriogram—anterior in two and inferior in six. A mean (range) of 3·1 (1–5) grafts were used, including an internal mammary artery to left anterior descending coronary artery in 16 and to the right coronary artery in one. The interval between bypass grafting and the second catheterisation ranged between six and 695 days. All grafts were

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patent at restudy, and in no case was there any clinical, cardiographic, or enzyme evidence of intraoperative myocardial infarction. No patient had chest pain, ST segment change, or other evidence of acute myocardial ischaemia at the time of either study.

Angiograms were performed in the 30° right anterior oblique position at a frame rate of 50/s. Angiograms were calibrated with a rule exposed at mid-chest level. We did not study extrasystoles or postextrasystoles, and we calculated left ventricular volume using the area-length method for each cavity outline.[4] Curves of ventricular volume versus time were smoothed with a three point moving average filter. We derived peak rates of left ventricular ejection and filling from this curve.

To quantify the extent and timing of regional wall motion 40 equally spaced points were identified by computer around the cavity outline with maximum area, and from each of these points the nearest point on the end systolic (minimum area) outline was identified.[5] From each of the 40 lines thus identified, a plot of inward or outward endocardial motion against time was constructed. All 40 plots were combined to form a contour display (figure). Plots numbered 7–20 represent the inferior wall and 21–40 the free wall. Those from 1 to 6 represent the region of the mitral valve, and we disregarded them in assessing left ventricular wall motion. On each of the contour plots we identified the times of maximum and minimum cavity area and the onset of mitral valve opening, taken as the frame in which unopacified blood first appeared within the cavity. As in a previous study,[6] we used an objective method to identify the onset of inward endocardial motion at the start of ejection. This was the beginning of a 100 ms period in which an inward velocity of at least 1 cm/s was maintained throughout, starting during a time window stretching from 50 ms before the time of peak ventricular volume to mitral opening. This calculation was performed individually for each of the 40 segments around the cavity outline and the onset of motion was marked on the contour display. We noted the timing of peak inward wall motion for

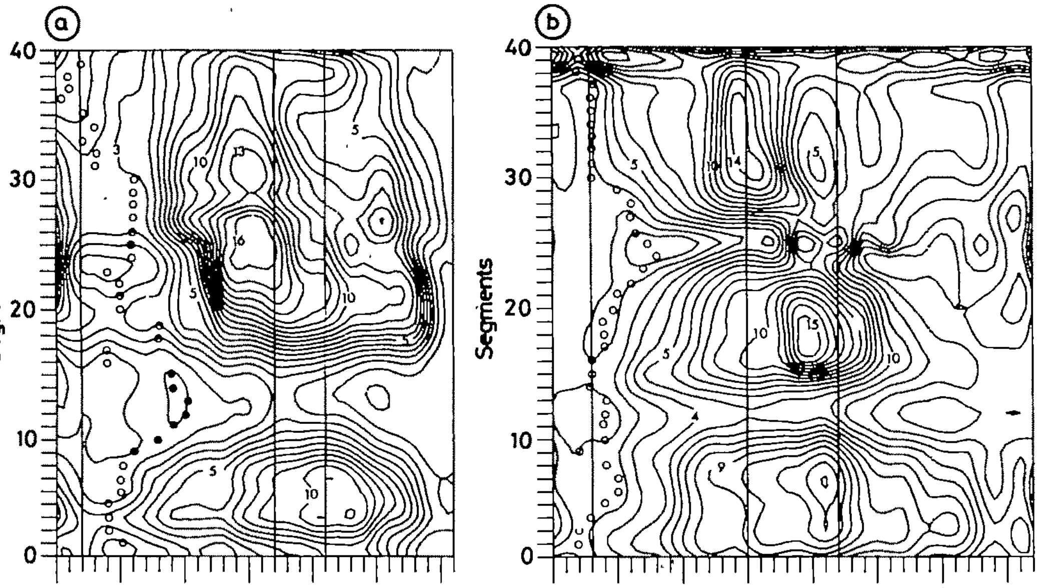

Fig (*a*) *Contour display before operation from a patient with coronary artery disease. Contours represent endocardial position in 1 mm steps. Vertical lines represent maximum and minimum cavity volume and mitral valve opening. Circles represent the onset of inward motion for each segment, calculated as described in the text. Open circles indicate values within normal 95% confidence limits for the region; closed circles are values showing abnormal delay. The display indicates abnormal delay in the onset of inward motion in segments 10–15. The delay between the onset of inward motion in the earliest and latest segments around the cavity outline is increased to 200 ms. Segments 11–15 also show hypokinesis. Zero time is arbitrary. (b) Contour display from the same patient after operation. The timing of the onset of inward wall motion is now normal, and significant hypokinesis is no longer present. The time interval from earliest to latest onset of inward motion has dropped to 100 ms. At the same time abnormal inward wall motion during isovolumic relaxation has now appeared in segments 17–23 associated with outward motion in segments 28–37.*

each segment in question, noting any values outside these limits.

We considered hypokinesis to be present when the overall amplitude of inward motion over three or more contiguous segments was less than the previously determined[6] lower limit of normal for 95% confidence interval. We identified abnormalities of isovolumic contraction[7] and isovolumic relaxation[5] as previously described.

STATISTICAL ANALYSIS

Differences in mean values were compared by Student's *t* test either for groups or for paired values from the same patient before and after operation as appropriate. Values are expressed as mean (1 SD) throughout.

Results

OVERALL LEFT VENTRICULAR FUNCTION

The table gives the results in detail. Mean values for ventricular volumes, ejection fraction, and peak ejection and filling rates were all within normal limits before operation. In two patients, values for ejection fraction were reduced; one had had an old anterior infarction (ejection fraction 47%) and the other an inferior infarction associated with cavity dilatation (ejection fraction 31%). There was no significant change between preoperative and postoperative values for end diastolic and end systolic volumes, ejection fraction, or peak filling or ejection rates either when mean values were compared or when changes in individual patients were assessed. The minor increase in filling rate did not achieve statistical significance either when group means were compared or when values in individual patients were considered.

AMPLITUDE OF WALL MOTION

There were regions of hypokinesis in six patients before operation affecting 5–15 segments (13 to 38% of the cavity outline). After operation these had resolved in three and were unchanged in three.

TIMING OF THE ONSET OF INWARD WALL MOTION

In 14 patients (mean (range) segments 4 (2–9)) the onset of inward wall motion was delayed with respect to the timing of maximum volume. In eight patients the mid-portion of the anterior wall was affected and in six the distal portion of the inferior wall. Values for these segments when considered individually were outside the normal 95% confidence interval, but they were surrounded on either side by a region of relative delay, leading to a characteristic pattern of "diagonal contours" (figure). We estimated the overall extent of this disturbance from the contour display, and found that it varied from six to 14, mean (SD) 9·3 (3·1) segments. After operation, the timing of the onset of wall motion returned to within normal limits in 12 cases, and in the remaining two patients there was a partial resolution (two segments each). In 13 patients the timing of the onset of inward wall motion with respect to maximum cavity volume was normal before operation. It remained so after operation in eight, but in five it became abnormal in 2–5 segments. Overall, the mean number of abnormal segments per patient dropped by 1·5 (2·8) after operation ($p < 0\cdot01$ in paired t test). This overall change was 2·1 (2·4) when only patients with abnormal segments before or after operation were considered ($p < 0\cdot001$). We also quantified the timing of the onset of inward motion by measuring the interval between its earliest and latest occurrence around the ventricle. Before operation this span was 190 (50) ms; it dropped to 130 (50) ms after operation. This fall was highly significant, whether taken as the difference between the mean values ($p < 0\cdot01$) or as individual changes ($p < 0\ 001$).

Table *Overall left ventricular function (mean (1SD))*

	Preoperative	*Postoperative*
End diastolic volume (ml)	120 (37)	110 (38)
End systolic volume (ml)	40 (24)	36 (21)
Ejection fraction (%)	69 (13)	68 (13)
Peak ejection rate (ml/s)	420 (150)	450 (220)
Peak filling rate (ml/s)	440 (140)	540 (260)

In five patients there was hypokinesis and delayed onset of motion in the same or overlapping segments. There was isolated delay in the onset of motion in nine and isolated hypokinesis in only one who had an old inferior myocardial infarction. In 12 patients we found neither hypokinesis nor delay.

WALL MOTION DURING THE ISOVOLUMIC PERIODS

Outward wall motion was abnormal during isovolumic contraction in four patients before operation. After operation it resolved in three. It appeared de novo after operation in one. In two patients the inferior segments showed delayed inward motion during isovolumic relaxation; in both this was relieved by operation. There was early outward wall motion during isovolumic relaxation in three patients; it was unaffected by surgery in all. It appeared after operation as a new finding in three — along the anterior wall in one (figure) and the inferior wall in two. In one case abnormal outward motion during isovolumic contraction was accompanied by overall hypokinesis but, otherwise, abnormal motion during the two isovolumic periods was independent of hypokinesis or asynchrony during systole. Abnormalities in the extent of wall motion during isovolumic relaxation did not alter the timing of peak inward wall motion, which was within normal limits for all patients before operation and remained so after surgery.

Discussion

PREOPERATIVE FINDINGS

Overall left ventricular function was well preserved in our patients: mean values for ventricular volumes, ejection fraction, and ejection and filling rates were all within normal limits. Even regional amplitude was preserved in all but six of the 27 patients, so that wall motion was normal on the basis of conventional angiographic analysis in most patients. When we used frame by frame analysis of angiograms to detect complex disturbances of timing, we identified abnormal function in more than half. This consisted of regional delay in the onset of inward motion, which we documented using objective criteria that took normal variation in timing into account. On the contour display the transition between normal regions and those showing delay in the onset of inward motion was not abrupt, but a recognisable pattern of diagonal contour lines was present, indicating gradual transition between the two. The whole disturbance affected nearly one quarter of the left ventricular cavity outline in the right anterior oblique projection. It was not consistently accompanied by any abnormality of wall motion during the two isovolumic periods, nor was the end of inward motion delayed. Thus even though overall left ventricular function was normal in these patients with angina pectoris caused by coronary artery disease, the timing of systolic wall motion was abnormal in most.

POSTOPERATIVE FINDINGS

The effects of successful coronary artery surgery were also consistent. Operation had no effect on ventricular volumes, ejection fraction, or peak rate of filling or ejection. It did, however, have a striking effect on the abnormal timing of wall motion. There was complete resolution in the delay in the onset of inward wall motion in 12 of 14 cases and partial resolution in the remaining two. Five new areas of abnormality appeared after operation, but these were less extensive, and overall there was a highly significant reduction in the number of abnormal segments. The improvement was even more clearly demonstrated when we quantified this asynchrony as the time interval between the earliest and latest onset of inward motion in different regions of the ventricle. After operation this interval fell by 30% to a value not significantly different from normal. Although there were disturbances of the two isovolumic periods of a type previously described in patients with chronic ischaemic heart disease,[5 7] these were not consistently affected by operation. The present study thus confirms previous results in demonstrating no consistent effect of coronary artery bypass grafting on overall left ventricular function in patients who did not have evidence of acute ischaemia at the time of the first ventriculogram.[2 8] Our observations are also compatible with previous echocardiographic studies on isovolumic wall motion that failed to demonstrate any improvement with antianginal drugs.[9] An effect of coronary bypass surgery in improving on the synchrony of ventricular wall motion during ejection has not received prominence in published reports, but the fact that it is a consistent finding when specifically sought suggests that it may be of pathophysiological importance.

In the present study we used contrast angiography because of its spatial resolution and frame rate. It does, however, have well documented disadvantages. We used only a single, right anterior oblique projection, so that we may have missed abnormalities in some cases. Although the overall extent of these disturbances of wall motion is considerable, the portion in which the onset of inward wall motion actually lies outside the normal limits is much smaller, so that when only the peripheral portion of the disturbance is demonstrated wall motion cannot be shown to be abnormal. It is also well recognised that the outer border of the ventricular cavity, as outlined by angiographic contrast medium, does not necessarily correspond to the position of endocardium.[10] This discrepancy is greatest at end systole, however, whereas the crucial observations in the present study were made at end diastole and early systole when there had been little inward wall motion. The same applies to the possibilities of translation of the heart in space and rotation about its long axis. Perhaps the major problem in interpreting the results comes when one tries to define normality. In studies such as this it is usual to take results from patients in whom overall left ventricular function and coronary arteriograms are normal and in whom no other important intracardiac abnormality has been demonstrated. Yet such individuals usually present with angina, which in many cases is indistinguishable clinically from that associated with obstructive coronary artery disease. Their suitability as the standard of comparison for a study such as the present one that investigates more subtle abnormalities of wall motion, quite possibly closely related to the symptom of angina itself, can obviously be questioned. We have no answer to this objection, and accept that using a compromised standard will make any detection system less sensitive by widening the normal 95% confidence interval. Single plane contrast angiography thus seems to be an adequate method for demonstrating the disturbances we have described, although it may well underestimate their frequency.

The characteristic delay in the onset of inward motion at the onset of ejection in the absence of outward wall motion during isovolumic contraction has previously been described in patients with coronary artery disease.[3] Its frequent occurrence under control conditions in regions that undergo akinesis during pacing induced angina and its predilection for the territory of the affected coronary artery in patients with single vessel coronary artery disease suggest that this behaviour is a marker of myocardium whose function is already compromised. The absence of outward wall motion during isovolumic contraction suggests that the timing of the onset of tension development was normal, with contraction initially isometric, indicating that the force generated was not great enough to cause inward motion. The absence of delay in the onset of outward wall movement demonstrates that the overall duration of contraction was normal. Its consistent improvement after bypass grafting confirms the close relation of abnormal wall motion to impaired blood flow and demonstrates its potential reversibility. Such behaviour can thus be regarded as a variant of "silent ischaemia", manifesting itself only by an abnormality of systolic wall motion without pain or even ST-segment change. Its response to revascularisation contrasts with the lack of change in segments moving abnormally during isovolumic contraction or relaxation, even when the two types of motion were present in the same ventricle.

A final question raised by these results is the nature of the link between abnormal wall motion and the symptom of angina. Angina occurs in conditions other than coronary artery disease. It is well recognised in hypertrophic cardiomyopathy and aortic stenosis, even when coronary arteriography shows the large vessels to be normal. It may thus be significant that in both these conditions similar studies of regional wall motion have demonstrated asynchronous onset of inward wall motion, unaccompanied by paradoxical outward motion during isovolumic relaxation or early ejection, and that in aortic stenosis this abnormality of wall motion is characteristically reversed by aortic valve replacement.[11 12] Angina and asynchronous wall motion are thus common factors in these two conditions, suggesting that the abnormal wall motion may be more than simply an independent marker of reduced coronary flow but may perhaps be more intimately related to the genesis of symptoms. Whatever the exact underlying mechanism, the present study gives some indication of the sensitivity of regional wall motion in identifying abnormal patterns of wall motion seen in patients with coronary artery disease, provided that the timing as well as the amplitude of wall motion is taken into account. It suggests that such methods might be used to complement these based on regional metabolism or electrical abnormality in order to elucidate the complex pathogenesis of clinical disturbances associated with myocardial ischaemia and coronary artery disease.

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Regional left ventricular wall motion in pacing induced angina

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SUMMARY Left ventricular cineangiograms (30° right anterior oblique projection) and high fidelity left ventricular pressure were recorded at rest in 10 individuals with normal hearts and at rest and during an episode of angina provoked by rapid atrial pacing in 14 patients with obstructive coronary artery disease. Angiograms were digitised frame by frame. The ventricular perimeter was divided into 40 segments and regional ventricular function was examined by means of isometric and contour plots and by the construction of segmental pressure-wall displacement loops. In 10 patients 12 abnormal resting regions were identified. The commonest (11 regions) was delayed onset of inward endocardial motion during systole which was manifest by diagonal contour lines on the contour plot. Six regions (five with associated delay in onset of inward motion) showed resting hypokinesis. Angina was associated with the development of 19 new regions of abnormal wall motion in 12 patients. Fourteen of these regions of abnormality were thought to be primary events occurring as a consequence of ischaemia and five to be secondary events occurring in normally perfused regions of myocardium. Hypokinesis occurred in 12 regions, developing in a region with normal amplitude at rest in seven and as an extension of resting hypokinesis in five. In 10 out of 12 cases the region of hypokinesis developed in a region showing diagonal contour lines at rest. Asynchrony with delay in the timing of peak inward displacement relative to minimum volume occurred with angina in eight regions (in six cases concomitent with hypokinesis and in two cases in isolation). In contrast with hypokinesis the pattern of wall motion at rest did not permit regions developing asynchrony with angina to be identified.

Pressure-displacement loops show that regional hypokinesis is associated with reduced segmental work and that regional asynchrony (delayed or premature timing of peak inward endocardial displacement) is associated with a loss of efficiency of energy transfer between the myocardium and the circulation. These observations illustrate the complex nature of wall motion abnormalities occurring with angina.

Regional myocardial ischaemia is believed to develop during episodes of angina in patients with coronary artery disease. A well documented consequence of ischaemia is hypokinesis in the affected region which can be demonstrated by contrast or radionuclide angiography.[1 2] Because most of these studies have used a two frame technique, in which only end systolic and end diastolic frames are examined, regional asynchrony (abnormal timing of wall motion) cannot be recognised and documented although it is well known as a consequence of experimental ischaemia.[3 4]

In this study we have used frame by frame analysis of left ventricular contrast cineangiograms to analyse the effects of an episode of angina on both the amplitude and timing of regional left ventricular wall motion. By constructing segmental pressure wall-displacement loops[5] we have been able to explore the physiological consequences of the regional hypokinesis and asynchrony that develop with angina on energy transfer from the myocardium to the circulation.

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Patients and methods

PATIENTS AND THE CATHETERISATION PROCEDURE

Studies were performed during diagnostic cardiac catheterisation in 24 patients being investigated for the symptom of chest pain thought to be angina. Patients gave written consent to the study that had been approved by the ethics committee of the Brompton Hospital. There were two groups of patients. One group comprised 14 men (mean age 51 years, range 42–68 years) with chronic stable exertional angina. Six of these patients had had previous myocardial infarction. Coronary arteriography showed that all had obstructive (>70%) coronary artery lesions (eight single, one double, and five triple vessel disease). The other group comprised 10 individuals (six men, four women, mean age 50 years, range 32–62 years) who proved to have a normal coronary arteriogram. All patients in this group had normal electrocardiograms, chest *x* rays, and M mode and cross sectional echocardiograms and they were therefore considered to be a control group with normal left ventricular function.

Catheterisation was performed from the right femoral artery and vein using the Seldinger method. Immediately after arterial cannulation heparin (50 u/kg) was given. Multiple views of the coronary arteries were obtained by Judkins' technique. After coronary arteriography an 8 French gauge Gaeltec catheter was positioned in the left ventricle by the long sheath technique.[6] The Gaeltec catheter combines a tip manometer with a fluid filled lumen which is used for calibrating the micromanometer and for injection of radio-opaque contrast material. Left ventriculography with a cine speed of 50 frames a second was performed in the 30° right anterior oblique projection with 50 ml of Urografin injected at a flow rate of 12 ml/s. High fidelity left ventricular pressure was recorded during contrast injection.

In the 14 patients with coronary artery disease an episode of angina was provoked by rapid atrial pacing with a Zucker bipolar catheter positioned in the right atrial appendage. Pacing was started at 100 beats per minute and increased by 10 beats per minute every two minutes up to a maximum of 150 beats per minute. The patients were asked to indicate the level of angina at which they would normally discontinue activity or stop to take a glyceryl trinitrate tablet. At this point atrial pacing was abruptly terminated and, within 5–10 seconds, a second left ventricular cineangiogram was performed, with the patient in sinus rhythm and with the same radiographic projection, quantity of contrast material, and flow rate as before. In all studies 15 minutes were allowed to elapse between coronary arteriography and left ventriculography. In the patients with coronary artery disease a further 15 minutes were allowed to elapse between initial ventriculography and the onset of atrial pacing.

The angiograms were calibrated by measuring the movement of the catheter tip when the catheter table was displaced by 10 cm.

ANALYSIS OF DATA

Cineangiograms were digitised frame by frame with a hand held cursor.[7] Frames were related to each other by a fixed external reference point. Beats chosen for analysis had occurred within five cycles of the onset of radiographic contrast medium first entering the ventricle. Extrasystoles and postextrasystoles were excluded from analysis. The end diastolic frame was identified by a QRS complex marker produced by an electrocardiographically gated light emitting diode in the shutter plane assembly of the cine camera. Cavity volume was determined by the area-length method.[8] The time of mitral valve opening was estimated to occur when unopacified blood first entered the left ventricle during diastole.

To study regional wall motion the end diastolic frame was divided into 40 separate points, or segments, equally spaced around the perimeter of the left ventricular cavity. The frame with the minimum area was taken and the points nearest to each of the 40 points on the end diastolic frame were identified. A line was then drawn between each pair of points. For each of the 40 lines a plot of endocardial position as a function of time was generated. For each of the forty lines thus generated we constructed a plot of endocardial position as a function of time. The 40 plots were combined to produce isometric and contour displays so that the amplitude and timing of wall motion for the ventricle overall could be appreciated.

A pressure-endocardial displacement loop was also constructed for each of the 40 segments. The area of such a loop is a measure of the external work performed during the cardiac cycle by that segment of the ventricle.[9] The maximum work that can be done by a segment working over the observed range of pressure and endocardial displacement is the product of the two—that is the area of the rectangle that just encloses the loop. The ratio (expressed as a percentage) between the measured area of the loop to the area of the rectangle just enclosing the loop is cycle efficiency. This is an index that relates energy transfer between the relevant region of the myocardium and the circulation.

We measured the following:

(*a*) Left ventricular end diastolic volume (synchronous with the onset of the Q wave on the electrocardiogram), minimum volume, and ejection fraction.

(*b*) Left ventricular peak systolic pressure and end diastolic pressure.

(*c*) For each of the forty perimeter points we measured the timing (to the nearest 20 ms) of onset of inward movement of endocardium relative to the end diastolic frame according to a previously described algorithm[10] and the timing of peak inward displacement of endocardium relative to the timing of minimum cavity volume.

(*d*) Overall amplitude of movement (to the nearest 0·5 mm) during the cardiac cycle for each of the 40 segments.

(*e*) For each of the 40 pressure-displacement loops we calculated segmental work (J/m^2) and cycle efficiency (%).

IDENTIFICATION OF ABNORMAL REGIONAL WALL MOTION

The angiograms and pressures recorded in the control group were used to derive normal values for the timing and amplitude of endocardial movement for each perimeter point and for work and efficiency for each segment.

In the patients with coronary artery disease: a region was considered to show *hypokinesis* if, in three or more adjacent segments, the amplitude of endocardial movement was below the lower 95% confidence limit of the range for the same segments in the control group; a region of *hyperkinesis* was identified when in three or more adjacent segments the amplitude of motion was above the upper 95% confidence limit; and a region of *asynchrony* was deemed to be present if in three or more adjacent segments the timing of endocardial motion was outside the 95% confidence limits of the range for the same segments in the control group.

Two types of asynchrony were identified: (*a*) delayed onset of inward endocardial motion during systole; (*b*) premature or delayed timing of peak inward displacement relative to the time of minimum cavity volume.

Table 1 *Left ventricular function*

	Controls (n = 10)	*Coronary artery disease (n = 14)*	
		Rest	*Angina*
LV systolic pressure (mm Hg)	149 (29)	141 (34)	146 (31)
LV end diastolic pressure (mm Hg)	16 (6)	23 (8)	27 (9)*
LV end diastolic volume (ml)	146 (47)	167 (37)	169 (38)
LV minimum volume (ml)	26 (13)	50 (31)	57 (32)*
Ejection fraction (%)	83 (3)	71 (12)	66 (14)†
Heart rate (beats/min)	71 (15)	69 (17)	80 (18)†

*p < 0·05. †p < 0·01 angina *vs* resting values.

STATISTICAL METHODS

Results are expressed as mean (1 SD). Differences between means were compared by Student's *t* test. We used linear regression to examine relations between variables.

Results

CONTROL GROUP

Pressure and volume (table 1)

In the 10 individuals with normal left ventricular function the left ventricular peak systolic pressure was 149 (29) mm Hg and left ventricular end diastolic

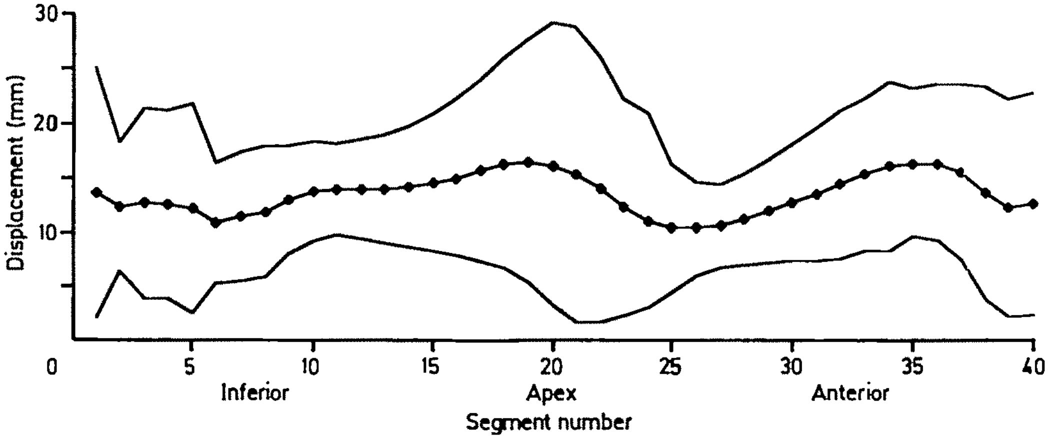

Fig 1 *Values for maximum endocardial displacement (mean (2 SD)) during the cardiac cycle for each of the 40 perimeter segments in the control group.*

pressure was 16 (6) mm Hg. Left ventricular end diastolic volume was 146 (47) ml, minimum volume 26 (13) ml, and ejection fraction was 83 (3)%. The heart rate during angiography was 71 (15) beats per minute.

Regional amplitude of wall motion

Figure 1 shows the amplitude of wall motion for each of the 40 segments. With a right anterior oblique projection and a fixed external reference point the overall amplitude of wall motion varies between different regions of the ventricle. The smallest amplitude of motion (10 (2)mm) was found in the apical and distal anterolateral segments (points 23–30) and the largest amplitude of motion (16 (4)mm) in the proximal anterolateral segments (points 33–37) and distal inferior segments (points 17–21).

Timing of regional wall motion

Figure 2 shows the timing of wall motion for each of the 40 perimeter points. Panel (*a*) shows the timing of onset of inward movement relative to end diastole. Panel (*b*) shows the timing of peak inward displacement relative to the time of minimum cavity volume. As with wall motion amplitude, regional non-uniformity is a normal finding, particularly for the timing of peak inward displacement relative to minimum cavity volume. In the control group peak inward displacement in inferior segments occurred up to 140 ms after minimum cavity volume, whereas in anterolateral segments peak inward displacement was seen up to 100 ms before minimum cavity volume. Inspection of the isometric display for an individual subject (fig 3a) makes this non-uniformity in the timing of peak inward displacement obvious. Except in the apical segments (17–26) there was much greater uniformity in the timing of inset of inward wall motion relative to the end-diastolic frame. This is most clearly shown on a contour display from an individual subject (fig 3b). Synchronous inward movement is shown by vertical orientation of the contour lines.

Pressure-displacement loops

Figure 4 shows the work (*a*) and cycle efficiency (*b*) of each of the 40 perimeter segments. Again regional non-uniformity was a normal finding. Regional efficiency ranged from 51 to 70% and was lowest in the proximal anterior segments (30–40).

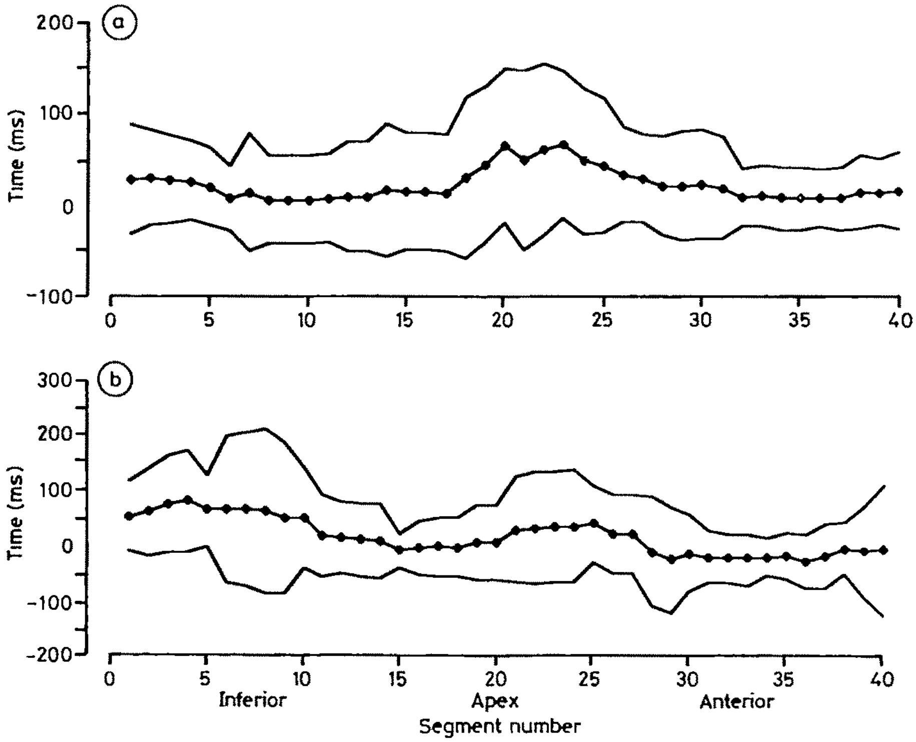

Fig 2 *Normal values (mean (2 SD)) for the timing of onset of inward endocardial displacement relative to end diastole (a) and of peak inward endocardial motion relative to minimum ventricular volume (b) for each of the 40 perimeter segments in the control group.*

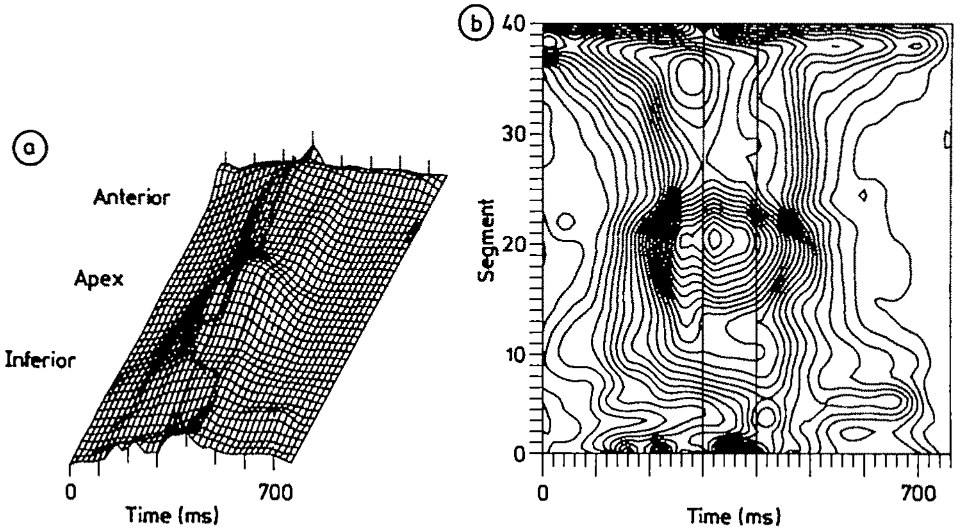

Fig 3 *An isometric plot (a) from a control. The display is produced by stacking, one above the other and slightly offset, the plots of wall displacement against time for each of the 40 segments. The diagonal lines are isochrones (20 ms intervals) linking points synchronous in time. The accentuated isochrones mark the timing of minimum ventricular volume (left side of plot) and the timing of mitral valve opening. The other accentuated line indicates the timing of peak inward movement for each segment and shows that regional non-uniformity is a normal finding. (b) A contour plot taken from a control. The contour lines (1 mm spacing) join points displaced by the same amount relative to their position at end diastole. The two vertical lines mark the timing of minimum cavity volume (left hand) and of mitral valve opening. In normal subjects the contour lines are closely spaced during ejection and early diastole and tend to run vertically.*

PATIENTS WITH CORONARY ARTERY DISEASE

Overall left ventricular function (table 1)

In the 14 patients with coronary artery disease, left ventricular systolic and end diastolic pressures at rest were 141 (34) mm Hg and 23 (8) mm Hg respectively. Resting left ventricular end diastolic volume was 167 (37) ml, ventricular minimum volume 50 (31) ml, and ejection fraction 71 (12)%.

An episode of angina produced small but statistically significant increases (4 (7) mm Hg ($p < 0{\cdot}05$)) in left ventricular end diastolic pressure and minimum volume (7 (11) ml ($p < 0{\cdot}05$)) and a fall in ejection fraction (5 (7)% ($p < 0{\cdot}01$)). Heart rate at rest was 69 (17) beats/min and during angina it was 80 (18) beats/min ($p < 0{\cdot}01$).

Amplitude and patterns of wall motion at rest

In four patients the amplitude and timing of wall motion at rest was within the normal range for all the 40 perimeter points. In the remaining 10 patients, 12 abnormal resting regions were seen. Late onset of endocardial motion during systole was the commonest abnormality and was seen in 11 regions in nine patients. The number of affected segments ranged from three to 10 (8–25% of cavity perimeter), with a mean of five segments. Delayed onset of inward wall motion was shown on the contour display by the diagonal (rather than the vertical) orientation of contour lines during early systole (fig 5). Six regions in five patients showed resting hypokinesis (mean number of affected segments nine (range 3–26). In all but one patient the region of resting hypokinesis occurred in a region that also showed late onset of inward endocardial motion.

No resting areas of abnormal timing of peak inward displacement relative to minimum cavity volume were identified.

Effect of angina on wall motion

The effects of an episode of angina on the amplitude and timing of left ventricular wall motion were complex. In two patients (one with a large area of resting hypokinesis and the other with normal wall motion at rest) no change was evident. In the remaining 12 patients 19 regions of abnormal wall motion developed with angina.

The commonest abnormality was the development of a region of hypokinesis in 12 regions in 10 patients. In seven instances hypokinesis developed in a region with normal amplitude of wall motion at rest. In the

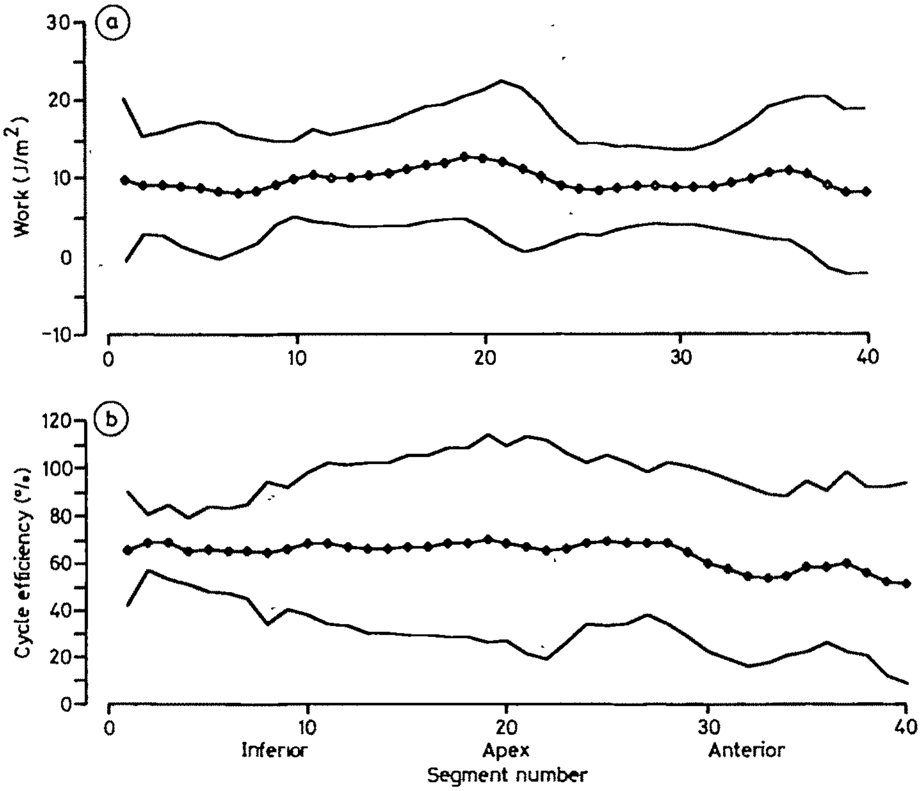

Fig 4 *Normal values (mean (2 SD)) for segmental external work (a) and cycle efficiency (b) for each of the 40 perimeter segments in the control group.*

remaining five cases there was extension (by at least four segments) of a resting hypokinetic region. In the 10 patients the mean number of affected segments was 7 (3), significantly greater than the control value of 2 (3) segments ($p < 0.001$). In all but two instances the region of hypokinesis developed within a region that at rest showed delayed onset of inward endocardial motion during systole (diagonal contour lines) (fig 6). A region of inferior hyperkinesis was seen in one patient with single vessel disease affecting the left anterior descending artery who developed a region of anterior hypokinesis. This was thought to be a secondary compensatory phenomenon.

A second major abnormality, asynchrony with delayed peak inward endocardial displacement relative to minimum ventricular volume, was seen in eight regions in eight patients (fig 7). In two of the eight patients the amplitude of wall motion in the affected region remained normal but in six hypokinesis was also present. In these eight patients with asynchrony the mean number of affected segments was 6 (2) ($p < 0.001$ *vs* control). The regions that developed asynchrony with angina were normal at rest in two cases, hypokinetic at rest in two cases, and showed late onset of inward endocardial motion at rest in four cases. Four of these eight patients also developed regions (mean number of segments 5, range 3–10) of premature peak inward endocardial displacement relative to minimum cavity volume elsewhere in the ventricle. Two of these four cases occurred in patients with single vessel disease. In these two cases the region of premature peak inward endocardial displacement was identified in a normally perfused region of myocardium. Premature peak inward displacement was thus thought to be a secondary phenomenon.

The development of new regions showing late onset of inward endocardial motion (or diagonal contours) was not a feature of an episode of angina. In the 14 patients the mean number of segments showing this abnormality was 4 (4) at rest and 4 (5) during angina (NS).

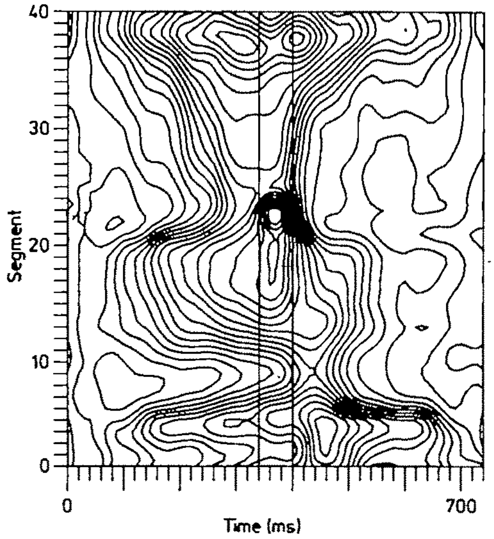

Fig 5 *A contour display derived from the cineangiogram at rest of a patient with coronary artery disease. The contour lines run diagonally in the inferior segments indicating delayed onset of inward endocardial motion in this region.*

Pressure-displacement relations at rest and with angina

Further physiological consequences of an episode of angina were identified from an analysis of the pressure displacement loops (table 2). In regions developing hypokinesis alone, segmental external work was reduced as a result of diminished amplitude of wall motion but cycle efficiency was conserved or even rose slightly. In regions showing asynchrony with delayed timing of peak inward endocardial motion the pressure-displacement loops became distorted (fig 8). The distorted shape of the loops reduced segmental cycle efficiency and hence segmental external work despite there being normal amplitude of wall motion in many instances.

In four cases the development with angina of asynchrony in a region of the ventricle subtended by a diseased coronary artery was accompanied by secondary abnormalities in a distant region of the ventricle with apparently normal coronary perfusion. These abnormalities which most obviously affected the proximal anterolateral wall took the form of premature timing of peak inward endocardial displacement which produced distorted pressure-displacement loops. As with asynchrony caused by delayed timing of peak inward endocardial displacement the result of such an alteration to the normal configuration of a pressure-displacement loop tended to reduce efficiency of energy transfer from the affected region of myocardium.

Relations between global and regional left ventricular function

Changes in regional left ventricular wall motion produced by an episode of angina showed little correlation with conventional global indices of left ventricular function. There was no relation between the number of segments developing asynchrony and changes in ejection fraction or left ventricular end diastolic pressure. Similarly, there was no relation between the number of segments developing hypokinesis and changes in left ventricular end diastolic pressure. Only the number of segments developing hypokinesis and the change in ejection fraction with angina showed a slight association ($r = 0{\cdot}7$, $p < 0{\cdot}05$).

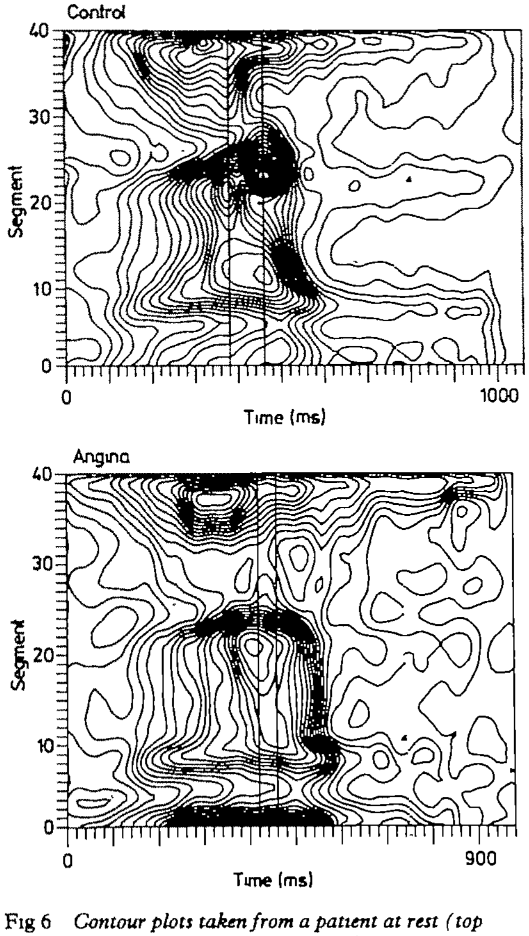

Fig 6 *Contour plots taken from a patient at rest (top panel) and during angina (bottom panel). Layout as in fig 3b. An anterior region of delayed onset of inward motion, shown by diagonal contour lines, is evident in the plot at rest. This became hypokinetic with angina.*

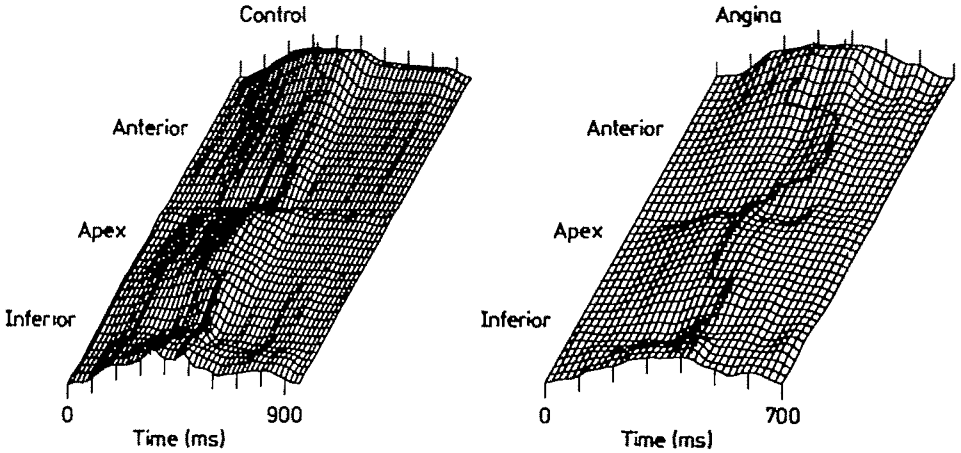

Fig 7 *Isometric plots taken from a patient at rest (a) and during angina (b). Layout as in fig 3a. An anterior region of asynchrony with delayed timing of peak inward endocardial displacement relative to minimum volume developed with angina. In some of these segments peak inward displacement occurred 80 ms after mitral valve opening.*

Discussion

This study shows that regional disturbances of left ventricular wall motion associated with pacing induced angina are complex, causing changes both in timing and amplitude of wall motion. The disturbances depend, in part, on the wall motion pattern present under control conditions. Left ventricular contrast angiography with frame by frame digitisation of cavity outlines seemed the technique most suited to illustrate such complex disturbances because it gives a comprehensive display of both the amplitude and the timing of regional wall motion.

During the normal cardiac cycle energy is transferred from the myocardium to the circulation. The amount of energy transferred depends not only on the amplitude of wall motion in the region in question, but also on the efficiency of energy transfer, which is influenced by the timing of regional motion. These aspects can be studied in detail by constructing pressure-displacement loops, similar to pressure-dimension loops which we have previously described.[8 9] It appears that local energy transfer may fall with angina either because the amplitude or the timing of regional wall motion becomes abnormal.

In most patients an episode of angina was associated with the development of abnormal wall motion. We cannot tell whether this was caused directly by the angina or whether there was a separate effect of the tachycardia used to provoke the angina and which persisted as a slightly higher heart rate at the time of the second angiogram. The commonest abnormality was a fall in amplitude (hypokinesis) which was seen in 10 patients. In four out of the five patients with single vessel coronary artery disease there was hypokinesis in the region subtended by the affected vessel, suggesting that it was the direct result of local ischaemia. Although regional work fell with hypokinesis, cycle efficiency, a measure of the synchrony of wall motion, was either unchanged or even increased slightly. In contrast, striking asynchrony appeared in eight patients, with peak inward wall motion being delayed relative to minimum cavity volume. In two cases this was so extreme that peak inward displacement in the affected region actually occurred in the period of rapid ventricular filling after mitral valve opening. The method of display we used might have been affected by the development of these wall motion abnormalities, since a reduction in local amplitude may have led to some redistribution of sites on the endocardium among the 40 lines along which motion was assessed. The disturbances themselves were extensive, affecting a mean of six or seven segments, so it is unlikely that this effect led to any major distortion in delineating them. Pressure-displacement loops demonstrated that asynchrony was associated with reduced external work as a result of diminished cycle efficiency, although in many instances the amplitude of wall motion in the affected segments remained normal.

Hypokinesis and delayed peak inward endocardial displacement occurring with angina both seemed to be direct consequences of local ischaemia. The remaining abnormalities, one region of hyperkinesis and four with premature peak inward endocardial motion, appeared different and seemed to represent

Table 2 *Analysis of pressure-displacement loops*

	Hypokinesis (n = 6)		*Asychrony with delayed peak inward motion (n = 8)*		*Asychrony with premature peak inward motion (n = 4)*	
	Rest	*Angina*	*Rest*	*Angina*	*Rest*	*Angina*
Efficiency (%)	58 (10)	63 (7)	73 (6)	64 (8)*	63 (19)	53 (16)
Work (J/m²)	5·7 (1·5)	3·7 (1·2)*	8·6 (1·7)	5·8 (1·7)*	6·4 (4·5)	5·8 (3·4)

*$p < 0·05$ angina *vs* rest.

secondary phenomena, because in patients with single vessel disease they developed in regions of the ventricle with normal perfusion. Similar disturbances have also been observed in patients with chronic coronary artery disease, where premature early outward motion is also found in regions with normal coronary supply and systolic function.[7] Despite this, premature peak inward displacement was associated with reduced cycle efficiency and therefore overall energy transfer in affected segments, underlining the generalised nature of the disturbance to overall left ventricular function that occurred during an attack of angina. In the present study only a slight fall in ejection fraction and increases in end systolic volume and end diastolic pressure were seen during angina, and it seems that orthodox measures of global left ventricular function do not reflect the extensive abnormalities that were documented from observations of regional wall motion.

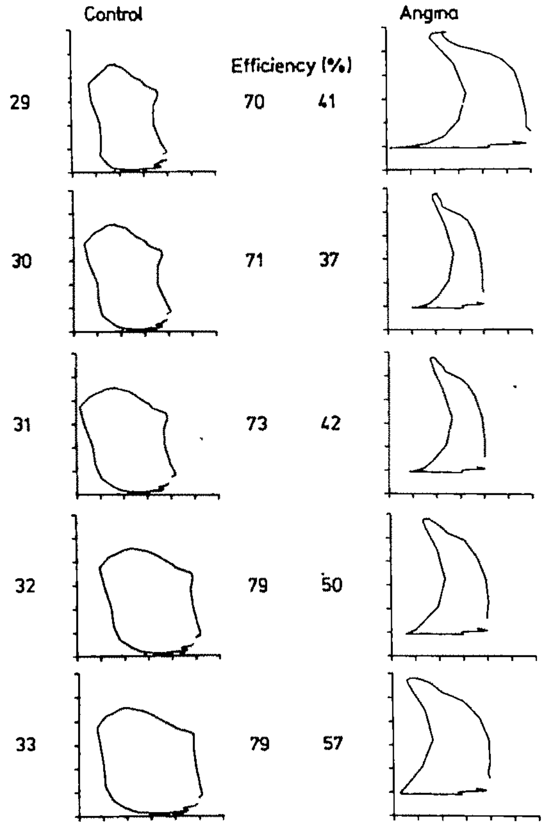

Fig 8 *A sequence of pressure-displacement loops (segments 29–33) taken from a patient who developed an anterior region of asynchrony with delayed timing of peak inward endocardial displacement relative to minimum ventricular volume. For each loop pressure is plotted on the ordinate and wall displacement on the abscissa. During angina (right hand panel) the loops are distorted and cycle efficiency is diminished.*

The pattern of wall motion during angina was related to that occurring under control conditions. In 10 out of the 12 regions of hypokinesis, with or without asynchrony, the angiogram at rest showed a pattern of diagonal contours in the affected region. The physical basis of this pattern is delay in the onset of inward endocardial motion, which in some regions did not begin until mid-ejection or even later. Such regions showed no outward movement during isovolumic contraction or early ejection; this strongly suggests that the timing of onset of tension development in these regions was normal, but that its magnitude was not great enough to cause inward wall movement until late in ejection when wall tension begins to fall. This delay was predominantly found in the mid-portions of the anterior and inferior walls where there is the least curvature and therefore wall tension is greatest for any given cavity pressure. The delay strongly suggests that even under resting conditions local function is compromised and that with an attack of angina this disturbance is simply accentuated. The distribution and time relations of this pattern of motion differ sharply from the early outward motion occurring during isovolumic contraction and early ejection that is found in some patients with chronic coronary artery disease in whom the pattern is confined to the apex and inferior wall and where the subsequent velocity and amplitude of inward motion may be quite normal and consistent with local delay in the onset of tension development.[11]

In sharp contrast to hypokinesis, asynchrony developing during angina arose either in normal regions or in those showing hypokinesis or delayed onset of inward motion during ejection. Its appearance could not, therefore, be predicted from the resting pattern of wall motion so that its development seems to involve some undetermined additional factor that appears only with stress. Once established, we speculate that the abnormality becomes self perpetuating because prolongation of myocardial tension development into early diastole would, of itself, further interfere with coronary flow to the affected region of myocardium.

This study confirms that attacks of angina were accompanied by regional disturbances of ventricular function. It has further demonstrated that these disturbances are complex, causing abnormalities in the timing as well as in the amplitude of wall motion. Two distinct mechanisms, hypokinesis and asynchrony, appear to be responsible and they can operate either separately or in combination. Regions that develop hypokinesis during angina can be predicted from analysis of the resting pattern of wall motion, suggesting that their function is already compromised at rest. Those in which asynchrony develops cannot be predicted in this way, which suggests that an additional factor operates in an attack of angina.

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Dyspnoea of cardiac origin in 67 year old men: (1) relation to systolic left ventricular function and wall stress

The study of men born in 1913

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SUMMARY The relation between dyspnoea of presumed cardiac origin and disturbed left ventricular systolic function was studied in a group of 67 year old men from the general population of Gothenburg, Sweden. Forty two men with cardiac dyspnoea were identified and 45 controls were randomly selected from a screened cohort of 644 men. Dyspnoea was graded according to the World Health Organisation standard, and M mode echocardiography, carotid pulse tracing, an apex cardiogram, and phonocardiography were used to evaluate the grade of dyspnoea and its relation to systolic time intervals, left ventricular ejection indices, and wall stress. The dyspnoea grade was significantly related to the left ventricular end systolic dimension, to septal and posterior wall fractional thickening, and to ejection indices such as fractional shortening. The dyspnoea grade was also significantly correlated with the ratio of end systolic wall stress to end systolic volume index. There was a close relation between end systolic wall stress and mean velocity of circumferential fibre shortening adjusted for heart rate. This relation did not clearly show reduced inotropy in the dyspnoeic men. There was no relation between the degree of dyspnoea and the systolic time intervals. Among the systolic variables obtained by echocardiography the only abnormal finding in mild to moderate dyspnoea was an increased end systolic dimension.

The grade of cardiac dyspnoea seemed to be related to the degree of systolic left ventricular dysfunction, which was considerably impaired in severe dyspnoea. In population studies left ventricular end systolic dimension and fractional shortening may provide sufficient information on systolic function without the need to assess variables that are independent of load.

In patients with congestive heart failure a large heart is associated with a poor prognosis,[1] and pronounced left ventricular dilatation identifies a subgroup at high risk.[2] The high mortality from congestive heart failure[3] emphasises the need for early detection and treatment as well as the need for a better understanding of the pathophysiological mechanisms.

New aspects of the non-invasive interpretation of systolic function—for example end systolic wall stress in relation to volume[4] and ejection phase indices[5]—have recently been examined. These indices are less influenced by loading conditions than are the traditional ejection phase indices, and so they may be better estimations of intrinsic myocardial properties and may relate better to symptoms of congestive heart failure.

Most of the current information on systolic cardiac dysfunction has been obtained from clinical studies on small groups of patients with symptoms. We have evaluated regional[6] and diastolic[7] left ventricular function in a random sample of 67 year old men from the general population of Gothenburg, Sweden. The purpose of the present study was to evaluate the relation between dyspnoea of presumed cardiac origin and various indices of systolic cardiac dysfunction in the same study population.

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Patients and methods

SCREENED POPULATION

The screened population[8] and the study population[6] have already been described in detail.

In 1980 a third of the male population in the city of Gothenburg born in 1913 (n = 817) was identified in the population register of the city and invited to a screening procedure for the evaluation of various aspects of dyspnoea. Six hundred and forty four men (79%) participated.

Dyspnoea was graded according to the World Health Organisation's modification[9] of the questionnaire that was proposed by the British Medical Research Council's committee on the aetiology of chronic bronchitis. Accordingly, dyspnoea was classified as no shortness of breath (grade 0), shortness of breath when hurrying on level ground or walking up a slight hill (grade 1), shortness of breath when walking with other people of own age on level ground (grade 2), having to stop for breath when walking at own pace on level ground (grade 3), and shortness of breath when washing or dressing (grade 4). The responses were checked by a physician during the interview that accompanied the physical examination.

Information on swollen legs at the end of the day and dyspnoea at night was obtained by interview. Information on chest pain was obtained by Rose's questionnaire.[9] The responses were evaluated by a physician and classified as no angina pectoris, possible angina, or definite angina. For this study, possible angina and definite angina were regarded as angina pectoris. Information on sustained myocardial infarction was obtained from the infarction register covering the city of Gothenburg.[10] Information on chronic bronchitis, asthma, cough, phlegm, and wheeze was obtained by interview. Smoking habits were recorded and total amount of tobacco smoked during life was calculated. One cigarette was assumed to be the equivalent of 1 g of tobacco.

A physical examination was performed by one of three physicians who were trained to make similar clinical judgements. Pulmonary rales and rhonchi were noted. The presence or absence of atrial fibrillation was coded from a standard 12 lead electrocardiogram.

STUDY POPULATION

In the screened population 142 (22%) out of 644 men had dyspnoea grade 1–4. Dyspnoea of cardiac origin was suspected in dyspnoeic men who (*a*) had either angina pectoris or other heart disease, leg oedema at the end of the day, dyspnoea at night, pulmonary rales, or atrial fibrillation and who (*b*) did not have a history of chronic bronchitis, asthma, cough with phlegm and wheeze, or rhonchi at the examination. Forty nine (35%) men with dyspnoea fulfilled these criteria. Four of these men died from ischaemic heart disease before an echocardiographic investigation could be performed, another two declined to participate, and one echocardiographic investigation was not interpretable. Of the 42 men remaining, 20 had grade 1, 12 had grade 2, five grade 3, and five had grade 4 dyspnoea. In the four dyspnoea grade groups digitalis/diuretics/β blockers were given to 9/1/8 (of 20) men with grade 1 dyspnoea, 4/1/6 (of 12) with grade 2 dyspnoea, 3/0/2 (of 5) with grade 3 dyspnoea, and 3/2/0 (of 5) with grade 4 dyspnoea.

Non-dyspnoeic men from the screened population born on day 6 of each month (n = 51) were studied as a control group. Of these 51 men, one died from a non-cardiac cause before the non-invasive investigation, four declined to participate, and one had an echocardiogram that was not interpretable. The remaining control group of 45 men without dyspnoea was divided into two subgroups. There were 14 men (group A) who were not and had not been treated for hypertension, had no atrial fibrillation, no angina pectoris, no myocardial infarction, and had no other known cardiac disease or any akinetic segments on cross sectional echocardiography; the remaining men (n = 31) are called group B. Six men in the control group B were on β blockers (none in group A); nobody in the control groups was on digitalis or diuretics.

No haemodynamically important organic valvar lesions were found by echocardiography or phonocardiography in any of the 87 subjects in the study population. Left ventricular aneurysms were found on cross sectional echocardiography in two men with grade 2 dyspnoea. They were excluded from the M mode echocardiographic study. No left bundle branch blocks were found, but one man with an implanted pacemaker was excluded from measurement of systolic time intervals.

METHODS

Dyspnoeic men and control subjects were investigated in random order and all information was coded blindly.

Systolic and diastolic blood pressures and heart rate were measured after approximately 45 minutes of supine rest. A phonographic method was used with a microphone placed over the brachial artery. The Korotkoff sounds were recorded together with lead II and a calibration signal from a mercury manometer, on a Mingograph. The blood pressure was measured to the nearest 1 mm Hg. The presence of Q waves was noted on a 12 lead electrocardiogram recorded at a speed of 50 mm/s and coded according to the Minnesota Code.[9] The codes 1:3, 1:2, and 1:1

were used and given one, two, and three points respectively.

An upright bicycle exercise test was performed with the load increased by 10 W each minute. At a spirometry test, pulmonary function was measured as vital capacity, and as the ratio of forced expiratory volume during one second to vital capacity. *X* rays of the chest were obtained during inspiration from a frontal, a lateral, and two oblique views. The films were interpreted by two experienced radiologists, who had no other information about the participants. Relative heart volume (ml/m^2 body surface area) was calculated, and venous congestion was estimated and coded as absent or present.

Non-invasive heart measurements

Detailed descriptions of non-invasive heart measurements and recording techniques are given elsewhere.[11-13]

Cross sectional echocardiographic recordings of routine views were stored on a videorecorder with playback and slow motion facilities and analysed for organic valvar disease and left ventricular wall motion disturbances.[6] M mode echocardiographic recordings were obtained at a paper speed of 50 mm/s. A handheld 2·25 MHz transducer was used in combination with either an Irex II or Echoscan 30 ultrasonograph. A simultaneous electrocardiogram (lead II) and a phonocardiographic tracing of the second heart sound was obtained on all M mode recordings.

The following measurements (leading edge to leading edge method) and calculations were made on three beats on the M mode tracings:

(*a*) The left ventricular diameter, interventricular septal thickness, and posterior wall thickness were all measured at end diastole (the electrocardiographic Q wave); and at end systole (the shortest distance between the septum and posterior wall at or before the initial vibrations of the second heart sound).

(*b*) Fractional thickening of the left ventricular wall was calculated as septal and posterior wall increase of thicknesses during systole divided by the corresponding diastolic thicknesses.

(*c*) Fractional shortening was defined as the difference between left ventricular diastolic and systolic dimensions divided by the diastolic dimension. Ejection fraction was calculated according to the cube formula, for reasons discussed elsewhere.[7] The mean velocity of circumferential fibre shortening (mean Vcf) was calculated as fractional shortening divided by left ventricular ejection time. The mean Vcf adjusted for heart rate (mean Vcf$_c$) was calculated as fractional shortening divided by left ventricular ejection time normalised by the square root of the cardiac cycle length in seconds.[5]

(*d*) Left ventricular meridional end systolic wall stress (10^3dyn/cm^2) was estimated as wall stress = $(1{\cdot}332 \times \text{pressure} \times D)/(4h \times (1 + h/D))$ where D is the left ventricular end systolic dimension and h is the mean of the septal and posterior wall end systolic thicknesses.[12 14] Pressure was obtained by estimating end systolic blood pressure from carotid pulse tracing, where systolic and diastolic blood pressures were assigned to the peak and nadir of the carotid curve, respectively, and end systolic blood pressure was estimated by linear interpolation to the height of the dicrotic notch.[12 15]

(*e*) Left ventricular peak emptying rate and time to peak emptying rate were calculated from the electrocardiographic R wave. Measurements were performed by means of a digitising table (Summagraphics ID-2CTR-TAB17, Connecticut, USA) and a microcomputer (Professional-380, Digital Equipment Corp) with a specially designed computer program.

(*f*) Measurements from pulse tracings were performed on five beats and the mean values were used. The left ventricular ejection time, the electromechanical interval, the pre-ejection period, and the isovolumic contraction time were measured, as previously described, from the simultaneous recordings of lead II, the phonocardiogram, and the carotid pulse tracing, or apexcardiogram.[11 12]

The electromechanical systole and left ventricular ejection time were related to heart rate. Left ventricular ejection time was therefore adjusted for heart rate according to the regression equation in control group A. The relative left ventricular ejection time was calculated as percentage of the expected normal left ventricular ejection time (control group A). We calculated the relations between pre-ejection period and isovolumic contraction time, on one hand, and left ventricular ejection time and left ventricular ejection time adjusted to heart rate 60 (division by the square root of the cardiac cycle length in seconds) on the other.

STATISTICAL ANALYSIS

Possible relations were tested with Pitman's non-parametric permutation test, which when applied to two groups is equivalent to Fisher's test. We used multiple linear regression technique for multivariate analyses. P values <0.05 were regarded as statistically significant.

Results

Table 1 shows the characteristics of the four groups (dyspnoea grade 1, 2, and 3 amalgamated). There was a significant relation between dyspnoea grade and weight, body mass index, lifelong tobacco con-

Table 1 *Characteristics (mean (SE)) of control groups and dyspnoeic groups*

	Control groups		*Dyspnoeic groups*		
	(A)	*(B)*			*Relation to dyspnoea grade (0–4)*
Dyspnoea grade	*0*	*0*	*1–3*	*4*	*(n = 87)*
Cardiac disease	–	+	+	+	*p for trend*
	(n = 14)	*(n = 31)*	*(n = 37)*	*(n = 5)*	
Weight (kg)	74 (3)	78 (2)	82 (2)	87 (4)	0·0078
Length (cm)	174 (1)	176 (1)	175 (1)	171 (1)	0·3870
Body mass index (kg/m²)	24 (1)	25 (1)	27 (1)	30 (1)	0·0011
Tobacco consumed (kg)	135 (37)	115 (23)	182 (24)	256 (69)	0·0079
Treated hypertension (%)	0	42	54	40	0·2954
Angina pectoris (%)	0	3	51	40	0·0001
Myocardial infarction (%)	0	16	32	20	0·0494
ECG Q waves (%)	0	16	38	60	0·0011
Atrial fibrillation (%)	0	3	11	20	0·2769
Congestion *x* ray (%)	0	3	11	60	0·0003
Heart size *x* ray (ml/m²)	403 (14)	414 (12)	428 (13)	544 (75)	0·0074
Maximum workload (W)	128 (5)	130 (5)	109 (5)	86 (2)	0·0001
Vital capacity (l)	4·4 (0·2)	4·3 (0·1)	4·0 (0·1)	3·4 (0·2)	0·0003
FEV%	69 (2)	66 (2)	69 (2)	77 (2)	0·0531

ECG, electrocardiographic, FEV%, forced expiratory volume during one second as percentage of vital capacity

Table 2 *Systolic time intervals (mean (SE))*

	Control groups		*Dyspnoeic groups*		
	(A)	*(B)*			*Relation to dyspnoea grade (0–4)*
Dyspnoea grade	*0*	*0*	*1–3*	*4*	*(n = 87)*
Cardiac disease	–	+	+	+	*p for trend*
	(n = 14)	*(n = 31)*	*(n = 37)*	*(n = 5)*	
Heart rate (beats/min)	59 (2)	63 (3)	61 (2)	76 (7)	0·243
Q-A2 (ms)	417 (7)	412 (6)	411 (6)	366 (8)	0·032
LVET (ms)	315 (6)	303 (6)	299 (5)	272 (19)	0·047
PEP (ms)	102 (3)	110 (3)	112 (3)	94 (12)	0·649
EMI (ms)	38 (5)	42 (3)	42 (3)	40 (6)	0·831
ICT (ms)	64 (6)	67 (3)	69 (4)	54 (13)	0·372
LVET%	100 (1)	98 (1)	96 (1)	97 (6)	0·107
PEP/LVET	0·33 (0·01)	0·37 (0·01)	0·38 (0·01)	0·36 (0·07)	0·469
ICT/LVET	0·20 (0·02)	0·23 (0·02)	0·23 (0·01)	0·21 (0·06)	0·956
PEP/$LVET_c$	0·33 (0·01)	0·36 (0·01)	0·38 (0·01)	0·32 (0·05)	0·721
ICT/$LVET_c$	0·21 (0·02)	0·22 (0·01)	0·24 (0·01)	0·19 (0·05)	0·839

EMI, electromechanical interval, ICT, isovolumic contraction time; LVET, left ventricular ejection time, $LVET_c$, left ventricular ejection time normalised for the square root of the cardiac cycle length; LVET%, left ventricular ejection time as percentage of expected; PEP, pre-ejection period, Q-A2, electromechanical systole.

sumption, angina pectoris, sustained myocardial infarction, Q waves in the electrocardiogram, venous congestion on the *x* ray, maximum workload at the exercise test, and pulmonary vital capacity.

UNIVARIATE ANALYSES

Table 2 shows the systolic time intervals. The grade of dyspnoea correlated significantly only with the total electromechanical systole and the left ventricular ejection time. When left ventricular ejection time was adjusted for heart rate the relation to dyspnoea grade was no longer significant.

Dyspnoea grade was significantly related to left ventricular systolic dimension, septal and posterior wall fractional thickening, ejection indices, the ratio of wall stress to volume index, and peak emptying rate (table 3). To test the ability of the various systolic echocardiographic variables to detect early heart failure, the differences between the group with dyspnoea grade 1–3 and the control group A were tested for the variables shown in table 3. Only the end systolic dimension was found to be significantly ($p < 0·05$) different in the group with dyspnoea grade 1–3 and the control group A.

MULTIVARIATE ANALYSES

Fractional shortening and ejection fraction were the two factors from tables 2 and 3 that were most closely related to dyspnoea grade. Fractional shortening was selected for further analysis to find out to what extent systolic variables contribute to the variation in cardiac dyspnoea.

Table 3 *Variables derived from M mode echocardiography (mean (SE))*

	Control groups		*Dyspnoeic groups*		
	(A)	*(B)*			*Relation to dyspnoea grade (0–4) (n = 87) p for trend*
Dyspnoea grade	*0*	*0*	*1–3*	*4*	
Cardiac disease	—	+	+	+	
	(n = 14)	*(n = 31)*	*(n = 37)*	*(n = 5)*	
Heart rate (beats/min)	60 (3)	62 (3)	61 (2)	81 (5)	0·0780
Left ventricular dimension:					
Diastole (mm)	48·8 (1·1)	51·4 (1·2)	54·6 (1·6)	54·4 (2 6)	0 0620
Systole (mm)	31 8 (0·9)	33 4 (1·3)	37·3 (1·5)	44·1 (3·8)	0 0020
Wall fractional thickening:					
Septum	0·48 (0 09)	0·46 (0·04)	0 45 (0 04)	0·20 (0·09)	0·0276
Posterior wall	0·88 (0 08)	0 82 (0·04)	0·73 (0 04)	0·47 (0 04)	0·0020
Fractional shortening	0·35 (0 01)	0·35 (0 02)	0·32 (0 01)	0·19 (0 04)	0·0002
Ejection fraction	0·71 (0 02)	0·72 (0 02)	0·68 (0 02)	0 46 (0 07)	0 0001
Mean Vcf (circ/s)	1·10 (0 05)	1·18 (0 06)	1·09 (0 04)	0·70 (0 10)	0 0012
Mean Vcf_c (circ/s $s^{0·5}$)	1·12 (0 05)	1·17 (0·05)	1 09 (0·04)	0·64 (0·11)	0 0008
Mean Vcf_{me} (%)	100 (5)	111 (4)	106 (4)	77 (10)	0 0084
ESWS (10^3dyn/cm^2)	54·6 (5·1)	61·6 (5·1)	59 0 (4 6)	93·8 (14 2)	0 1720
ESWS/ESVI (10^3dyn/cm^2)/(ml/m^2)	3·22 (0·20)	3 12 (0·20)	2 92 (0·26)	1 97 (0 38)	0 0310
ESWS/ESVI × EF (10^3dyn/cm^2)/(ml/m^2)	2 30 (0 16)	2·30 (0 20)	2·11 (0·22)	0·97 (0·39)	0·0159
Peak emptying rate (mm/s)	93 0 (5·2)	101·3 (5 0)	92·3 (3 4)	70·4 (11·9)	0·0298
Time of R wave to peak emptying rate (ms)	150 (15)	163 (9)	162 (8)	194 (18)	0·2388

ESVI, end systolic volume index; ESWS, end systolic wall stress; Vcf, velocity of circumferential fibre shortening; Vcf_c, Vcf adjusted for heart rate; Vcf_{me}, Vcf measured as percentage of Vcf expected from the end systolic wall stress level (computed from the regression of control group A).

Table 4 *Results of univariate and multivariate analyses of the contribution of clinical and echocardiographical variables to the variance of dyspnoea grade*

	Univariate analysis			*Multivariate analysis*		
	r	*p*	*Proportion of explained variance*	*Additional proportion of explained variance*	*p*	*Cumulative proportion of explained variance*
Angina pectoris	0 51	<0 0001	0·26	0·27*	0 0001	0·27
Pulmonary congestion	0 46	0 0003	0 21	0·19	0 0001	0 46
Fractional shortening	0 41	0 0002	0 17	0 05	0 0058	0 50
Electrocardiographic Q waves	0 39	0 0011	0 15	0·02	0 0835	0 53

*The discrepancy with univariate analysis is the result of eight missing values in the multivariate analysis.

As a first step a multivariate analysis was performed of dyspnoea grade versus a history of angina pectoris, myocardial infarction, tobacco consumption, treatment for hypertension, blood pressure, heart size and pulmonary congestion at x ray examination, atrial fibrillation and Q waves in the electrocardiogram, and vital capacity. In this analysis angina pectoris, pulmonary congestion, and Q waves were significantly and independently related to dyspnoea grade, whereas the other factors were not.

The significant factors from the first analysis and fractional shortening were introduced in a new multivariate analysis to test their relation to dyspnoea grade (table 4). All the univariate relations were highly significantly related to dyspnoea grade. The right side of the table shows the multivariate analysis. Each of the variables, except for the Q waves, contributed significantly to the explanation of dyspnoea grade when the other variables were taken into account. The contribution of the Q waves was of borderline significance. About 50% of the variation in dyspnoea grade could be explained by the variables thus tested.

The clinical variables from table 4 were brought together into a clinical score in which the presence of angina, pulmonary congestion, and Q waves in the electrocardiogram were given one point each. Figure 1 shows the mean dyspnoea grade in groups of men

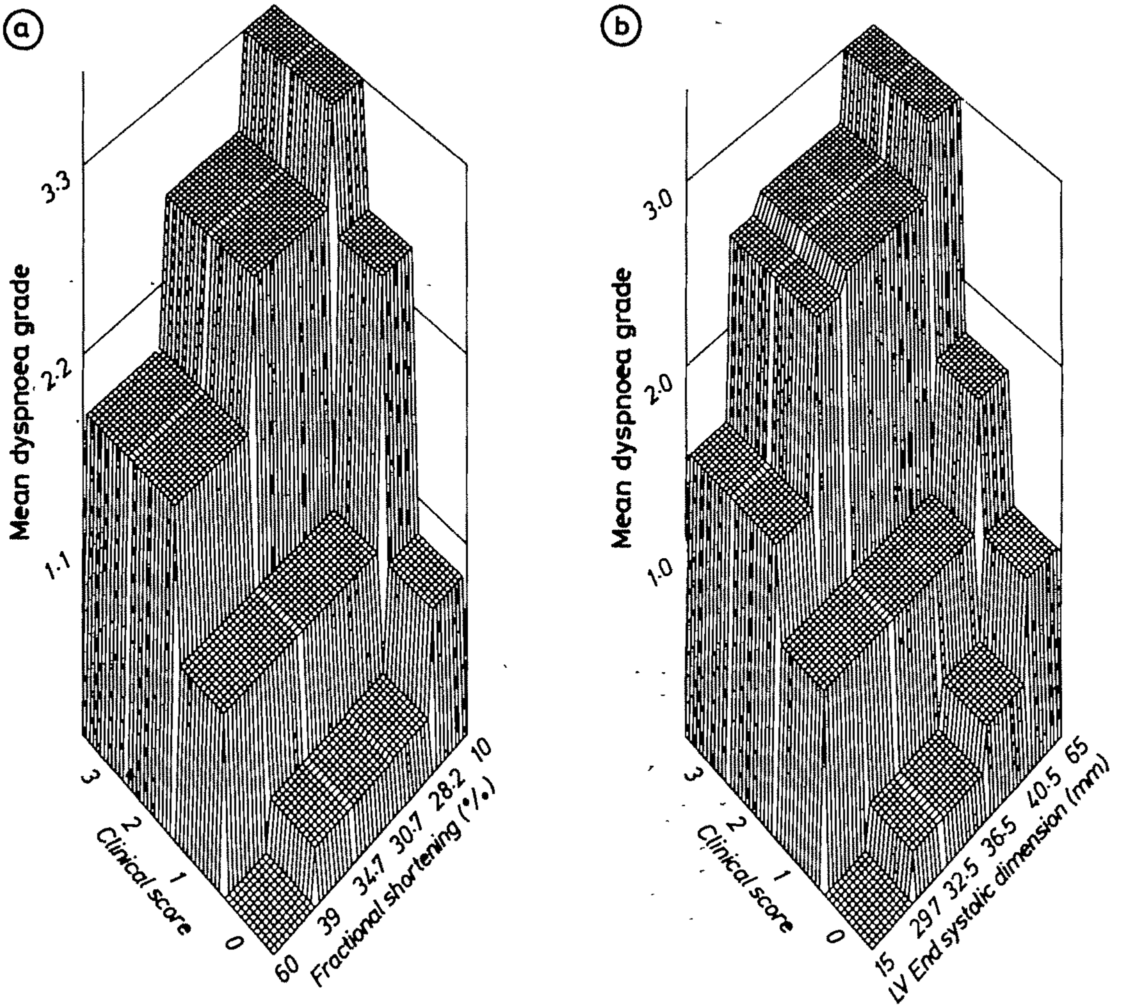

Fig 1 *Mean dyspnoea grade in groups distributed according to clinical involvement and quintiles of fractional shortening (a), or clinical involvement and quintiles of left ventricular (LV) end systolic dimension (b). Clinical involvement was indicated by one point for Q wave in the electrocardiogram, one point for pulmonary congestion on x ray, and one point for a history of angina pectoris. The points were summed as a clinical score. In groups with similar clinical involvement the grade of dyspnoea was related to fractional shortening and end systolic dimension.*

distributed according to the clinical score and fractional shortening (fig 1a) and according to the clinical score and left ventricular end systolic dimension (fig 1b).

LOAD DEPENDENCE

Table 3 shows the end systolic wall stress, the ratio of end systolic wall stress to volume index, and this ratio multiplied by the ejection fraction. Dyspnoea grade was significantly related to the last two ratios but not to end systolic wall stress (despite a high value for wall stress in the group with grade 4 dyspnoea). Figure 2 shows the relation between mean velocity of circumferential fibre shortening adjusted for heart rate (Vcf_c) and end systolic wall stress, where the confidence interval of control group A represents the normal relation between stress and shortening. Only three men (dyspnoea grade 4) had mean Vcf_c values below 2 SD of the value in the control group A. Of these three men, one had a low mean Vcf_c when account was taken of wall stress. We used the regression formula from control group A to calculate

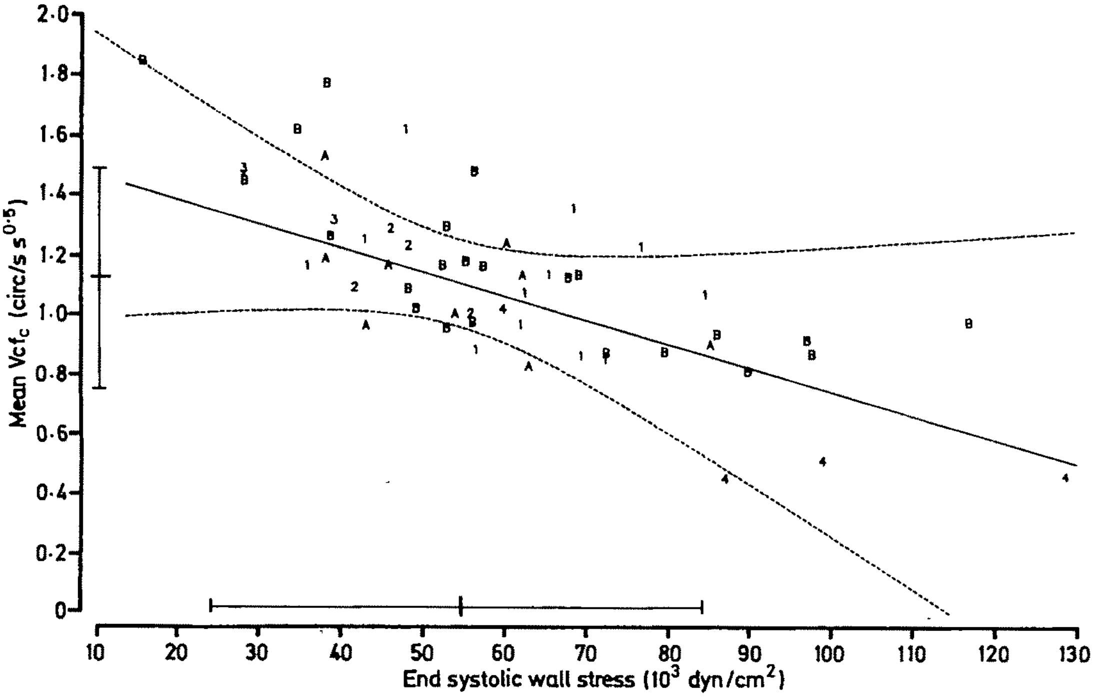

Fig 2 *The relation between mean velocity of circumferential fibre shortening adjusted for heart rate (mean Vcf$_c$) and end systolic wall stress. The curved lines represent 95% confidence limits for control group A. The horizontal line represents mean and confidence interval (± 2 SD) for end systolic wall stress and the vertical line the mean and confidence interval for Vcf$_c$ in the control group A. A shows volunteers in control group A, and B those in control group B; the numbers 1–4 show the corresponding grade of dyspnoea.*

the expected mean Vcf$_c$ from the wall stress value. Table 3 gives the ratios of measured to expected mean Vcf$_c$ as percentages (mean Vcf$_{c_{me}}$).

Discussion

We found impaired systolic function in dyspnoeic men from the general population. Dyspnoea was related not only to fractional shortening and to ejection fraction but to most other echocardiographic indices of systolic function.

In several studies the New York Heart Association functional classification has been used to grade congestive heart failure. The dyspnoea grade applied in this study was found to be more closely related to working capacity, heart size, pulmonary congestion, and other functional variables than the New York Heart Association function classes (unpublished data). Because of this we used the grade of dyspnoea in the present study.

Systolic time intervals have been shown to be of limited value for the study of cardiac function in coronary heart disease.[11] We support this view because we did not find any significant relation between dyspnoea grade and systolic time intervals in the present study. Recently it was suggested that left ventricular ejection time should be corrected for heart rate before calculating ratios—for example to the pre-ejection period.[16] We found, however, that such a recalculation did not affect the relation between dyspnoea grade and time intervals.

The M mode echocardiographic recordings of cardiac dimensions were obtained with a handheld single crystal transducer. Theoretically it is better to use cross sectional echocardiography to guide the positioning of the M mode beam; however, this did not improve either the accuracy or the reproducibility of left ventricular measurements.[17] When it is difficult to obtain a high quality M mode image, a single transducer in the hands of an experienced echocardiographer has advantages because when the echo window is small its smaller size facilitates angulation and the higher repetition frequency of the echo signal improves resolution. Cross sectional echocardiography was used to establish that the M mode tracings were adequate. We followed the suggestion in a study of wall stress in subjects with coronary artery disease[18] and excluded two men with left ventricular aneurysms. This should have made the indices of the ejection phase more representative. Major dyskinetic areas, which would have considerably limited the representativeness of the M mode recordings, were not found in the remainder of the patients.

The ejection fraction is the most commonly used index of systolic myocardial function. The calculation of ejection fraction from M mode echocardiography is based on assumptions of geometry, because the left ventricular volumes are computed from one ventricular dimension only.[19] We do not consider that the ejection fraction has any advantages over fractional shortening except that it is better known. The correlation between grade of dyspnoea and both these measures was similar, and we used fractional shortening for the multivariate analyses.

Ejection phase indices, although widely used as measures of left ventricular function, have their limitations because they are affected not only by changes in left ventricular contractility but also by changes in preload and afterload.[20,21] This load dependence is especially important in patients with valve dysfunction. In mitral regurgitation, for instance, favourable loading conditions caused by the low impedance leak into the left atrium may serve to maintain ejection indices near normal when the inotropic state is reduced.[4,13,20] On the other hand, in aortic stenosis subnormal fractional shortening may be caused by an increased afterload, and normal values of ejection phase indices may be found postoperatively. In the present study no subject had any signs of haemodynamically important valve disease.

Various alternative approaches have been proposed to overcome the fact that ejection phase indices depend upon loading conditions.[4,5,22] In most cases these are based on the relation between end systolic pressure or wall stress (measures of afterload) and ejection phase indices or end systolic dimension or volume.[4,5,15] The relation between afterload and ejection phase indices such as fractional shortening or mean velocity of circumferential fibre shortening is useful when studying the individual contractility to load matching.[5,12,15] The mean velocity of circumferential fibre shortening is augmented by an accelerated heart rate,[23] but the mean velocity of circumferential fibre shortening corrected for heart rate may be the measure of contractile performance that is least dependent upon preload.[5] The relations described are comparatively independent of preload, take account of the afterload, and are sensitive to the inotropic state.[4,24] The various relations have been used to evaluate contractile reserve in patients after cardiac transplantation,[25] to study the cardiac function in sickle cell anaemia with reduced afterload[26] and in hypertensive heart disease with an increased afterload,[12] and to evaluate the left ventricular mechanics in dilated cardiomyopathy[27] and in patients receiving antineoplastic agents.[28] Such indices have also been used to show that the hyperkinesia in hyperthyroidism is the result of augmented contractility rather than altered loading (or chronotropic) conditions,[29] and that the contractile state in young athletes is normal despite a considerable increase in left ventricular mass and irrespective of the type of exercise.[30] The ratio of end systolic wall stress to volume has been used to predict preoperatively the outcome of valve replacement.[4] Incorporation of ejection fraction into this index has been claimed to improve prognostic accuracy.[22]

In the present study two of the various proposed "load independent indices" were applied. Their correlations with the grade of dyspnoea were similar. The ratio of end systolic wall stress to volume correlated with the grade of dyspnoea, and the addition of ejection fraction to the formula had no appreciable effect. The relation between mean velocity of circumferential fibre shortening corrected for heart rate and dyspnoea grade was not improved by taking account of the level of wall stress. Three men (dyspnoea grade 4) had abnormal mean velocity of circumferential fibre shortening corrected for heart rate (below two standard deviations of the mean value of the control group A), and one of them seemed to have a reduced mean velocity of circumferential fibre shortening corrected for heart rate in relation to the wall stress level, indicating a non-compensated depressed inotropic state.

Consideration of preload and afterload is important, particularly in valve disease, and in pharmacological or other interventions aiming at the treatment or investigation of, for example, preload reserve. In a study of patients treated with doxorubicin, variables that are independent of load, such as the wall stress/fractional shortening relation, were regarded as useful for the early detection of left ventricular dysfunction.[28] In the present study such indices were not helpful in detecting early cardiac dysfunction, as judged by their relation with presumed cardiac dyspnoea. Pharmacological intervention to alter afterload during the investigation might have yielded some additional information and led to an early diagnosis of heart failure. The additional value of such an approach is not obvious,[28] however, and interventions in epidemiological studies are neither practicable or ethical.

Early systolic dysfunction causing dyspnoea seemed to be most effectively demonstrated by the end systolic dimension. The end systolic dimension was the only one of the variables tested that was significantly different in the control group A and the group with grade 1–3 dyspnoea. In this small group this variable was a better indicator of early systolic dysfunction than fractional shortening (and ejection fraction). The reason may be that any increase in systolic dimension was accompanied by an increase in diastolic dimension, thereby reducing the decrease of fractional shortening.

We conclude that the group with grade 4 dyspnoea made an important contribution to the relation between dyspnoea grade and echocardiographic variables. The group with grade 1–3 dyspnoea essentially seemed to have a well functioning ventricle. The only significant difference was an increase in end systolic dimension; heart rate, wall stress, and fractional shortening were normal (table 3). On the other hand, the group with grade 4 dyspnoea showed increased heart rate and wall stress and reduced fractional shortening. These considerable differences between those with grade 1–3 dyspnoea and those with grade 4 dyspnoea might indicate pathophysiological or haemodynamic differences between the groups. One explanation is that the influence of diastolic dysfunction is greater in early heart failure (grade 1–3). Because it has recently been suggested that diastolic abnormalities might be important in congestive heart failure when systolic function is normal we evaluated diastolic function in a separate study.[7]

Valve disease and severe untreated hypertension are the major mechanisms that alter the load in congestive heart failure; neither was present in this study population. Thus the loading conditions were not imposed externally but were brought about mainly by mechanisms generated to compensate for impaired myocardial function. Fractional shortening seems to be an appropriate simple measure of contractility in a population in whom clinical and noninvasive data indicate that congestive heart failure is caused by coronary artery disease. An increased end systolic dimension may be an even earlier sign of abnormal systolic function. Although several complex variables of systolic function have emerged during recent years, these indices do not necessarily add much information in population studies. Also, they do not lead to earlier detection of cardiac failure than simple measures such as end systolic dimension or fractional shortening.

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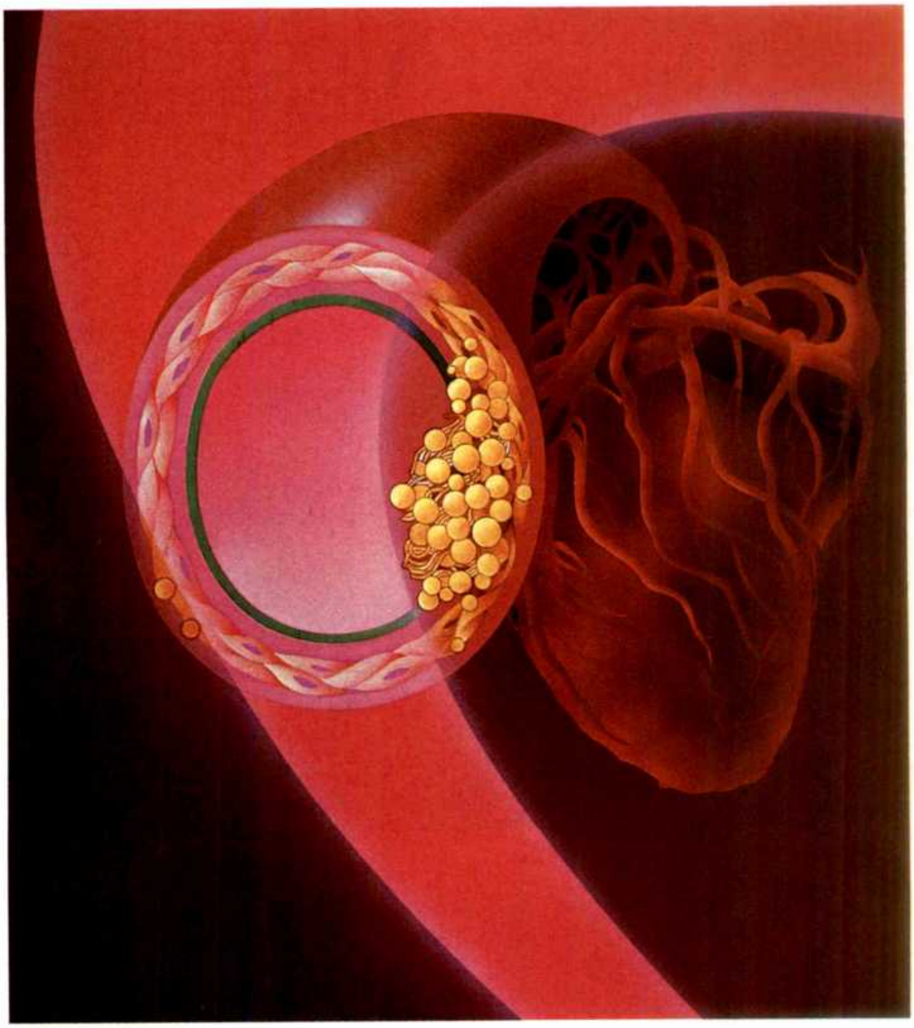

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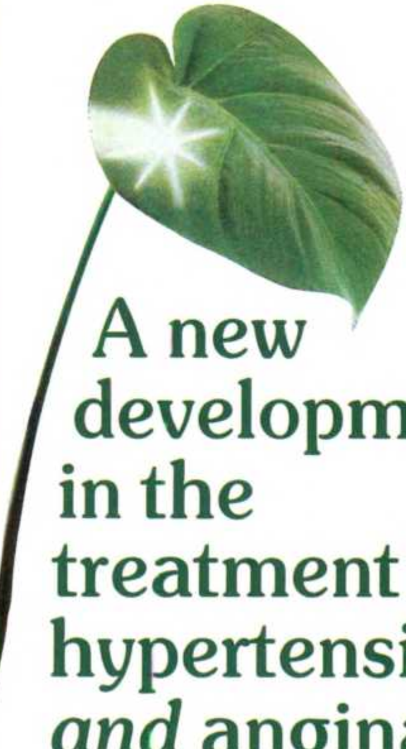

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Dyspnoea of cardiac origin in 67 year old men: (2) relation to diastolic left ventricular function and mass

The study of men born in 1913

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SUMMARY The relation of cardiac dyspnoea to diastolic left ventricular dysfunction was examined in a sample of 67 year old men from the general population of Gothenburg, Sweden. Forty two men with cardiac dyspnoea and 45 controls were selected from the screened cohort of 644 men. M mode echocardiography, apexcardiography, and phonocardiography were used to evaluate heart sounds, diastolic time intervals, aortic root motion (atrial emptying index); peak rate of change in left ventricular dimension, left atrial and ventricular size; and left ventricular mass. There was a significant relation between dyspnoea grade and left ventricular mass and posterior wall thickness. Dyspnoea grade also correlated significantly with the amplitude of the rapid filling wave and the third heart sound, atrial emptying index and left atrial size, the pulmonary component of the second heart sound, and the dimension of the right ventricle. In mild to moderate dyspnoea fractional shortening was normal, but posterior wall thickness and left atrial dimension were increased. The time from the second heart sound to the O point of the apexcardiogram, adjusted for heart rate, was significantly prolonged in mild to moderate dyspnoea, but not in severe dyspnoea. There was a significant decrease of rate adjusted isovolumic relaxation time, probably secondary to altered loading conditions, in severe dyspnoea, but not in mild to moderate dyspnoea. When the effect of systolic function was excluded multivariate analyses showed that the relation between dyspnoea grade and left atrial dimension persisted.

The finding that diastolic abnormalities of the heart contributed to the generation of cardiac dyspnoea may have implications for treatment.

The introduction of non-invasive methods has made detailed studies of cardiac function possible not only in the clinical situation but also in the general population.[1 2] Because early detection and treatment of cardiac dysfunction may be the best way to reduce the high mortality from congestive heart failure,[3] practicable methods of early detection would be valuable.

In recent years there has been an increase in the interest in, and understanding of, diastolic left ventricular function as an important part of cardiac performance.[4] Diastolic abnormalities of cardiac function often occur early in disease processes such as hypertension[2] and coronary heart disease.[5 6] Furthermore, it has been shown that impaired diastolic function is frequent in non-dilated coronary diseased hearts[7] and may cause congestive heart failure despite normal systolic function.[8 9]

The prevalence of diastolic abnormalities has been measured in patients with primary hypertension, coronary heart disease, and overt congestive heart disease, but not in the general population. We have already studied dyspnoea of presumed cardiac origin in a random sample of 67 year old men and the

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relation of this symptom to regional[10] and systolic[11] left ventricular function. In the present study we investigated whether there was any association between dyspnoea of presumed cardiac origin and impaired diastolic function in the same group of men.

Patients and methods

SCREENED POPULATION

The screened population[12] and the study population[10 11] have been described in detail elsewhere. Please see our earlier paper.[11] Dyspnoea was measured according to the World Health Organisation's modification of the questionnaire proposed by the British Medical Research Council's Committee on the Aetiology of Chronic Bronchitis.[13] Information on sustained myocardial infarction was obtained from the Myocardial Infarction Register covering the city of Gothenburg. Information on cardiac disease, chronic bronchitis, and smoking habits was obtained by questionnaire.[12]

STUDY POPULATION

Based on the dyspnoea questionnaire, the medical history, and a physical examination, 49 men were considered to have dyspnoea and a possible underlying cardiac disease but no signs or symptoms of obstructive pulmonary disease. Seven of these men were excluded from the study.[11] A control group of 51 men without dyspnoea was selected and 45 were eventually included in the study. Full details of these men are given in our earlier paper.[11] The control group was divided into two subgroups. Those in group A (n = 14) had no hypertension treatment, no atrial fibrillation, no angina pectoris, no myocardial infarction, and no other known cardiac disease or akinetic segments on cross sectional echocardiography. Group B was made up of the remaining men (n = 31). Six men in the control group B were on β blockers (none in group A), while no man in any of the control groups was on digitalis or diuretics.

METHODS

The investigations and coding of results are described in our earlier paper.[11] Electrocardiograms were classified according to the Minnesota Code.[13]

Non-invasive heart measurements

Detailed descriptions of our methods and recording techniques are given elsewhere.[1 2 14] and we followed the protocol of our earlier study.[11]

M mode echocardiographic left ventricular diameter, interventricular septal thickness, and posterior wall thickness were all measured at the P and at the Q waves of the electrocardiogram (lead II), and when the distance between the septum and posterior wall (at or before the initial vibrations of the second heart sound) was shortest. Unless specified, left ventricular dimension as well as septal and posterior wall thickness refer to the value at the Q wave. The right ventricular dimension was measured at the electrocardiographic Q wave.

We calculated the peak rate of change of left ventricular dimension before atrial contraction and the peak rate of posterior wall thinning during the same period. The time from minimum left ventricular dimension to peak left ventricular filling and the time from the most anterior excursion of the posterior left ventricular wall to posterior wall peak thinning were measured. Measurements were performed with a digitising table (Summagraphics ID-2CTR-TAB17, Connecticut, USA) a microcomputer (Professional-380, Digital Equipment), and a specially designed computer program.

The left ventricular mass was calculated by the cube formula, assuming a left ventricular muscle shell with the thickness of the mean of the septum and posterior wall. The Teichholtz formula,[15] was applied in a similar manner. Left ventricular mass (g) was estimated by subtracting the volume of the cavity from that of the total left ventricle and multiplying by 1·05, which is the specific gravity of heart muscle. The left ventricular mass was adjusted for body surface area. To validate the methods we compared the mass measurements at the P wave, Q wave, and end systole. Both formulas gave good correlations ($r = 0·98$ to $r = 0·94$), but because the mean values by the cube formula were less variable we used this formula for the present report. Fractional shortening was calculated as left ventricular (end diastolic − end systolic)/end diastolic dimensions.

The left atrium was measured at aortic valve closure or at the initial vibrations of the aortic component of the second heart sound. The mesurements were adjusted for body surface area.

The atrial emptying index[8 16] was calculated from the posterior aortic wall motion as an estimate of early left ventricular filling properties (fig 1). The point at which the aortic root had reached its most anterior position was taken as being equivalent to mitral valve opening. We measured the distance from this point to that at which atrial contraction had its initial effects on the aortic wall. The first third of this distance was marked. The atrial emptying index represents the relation between the aortic wall motion during this first third of the distance and the aortic wall motion during the full distance measured. In the case of atrial fibrillation, the initial QRS activity was used to mark the end of the passive filling period.

The isovolumic relaxation time (A2 − Mo) was calculated as the distance from the initial vibrations

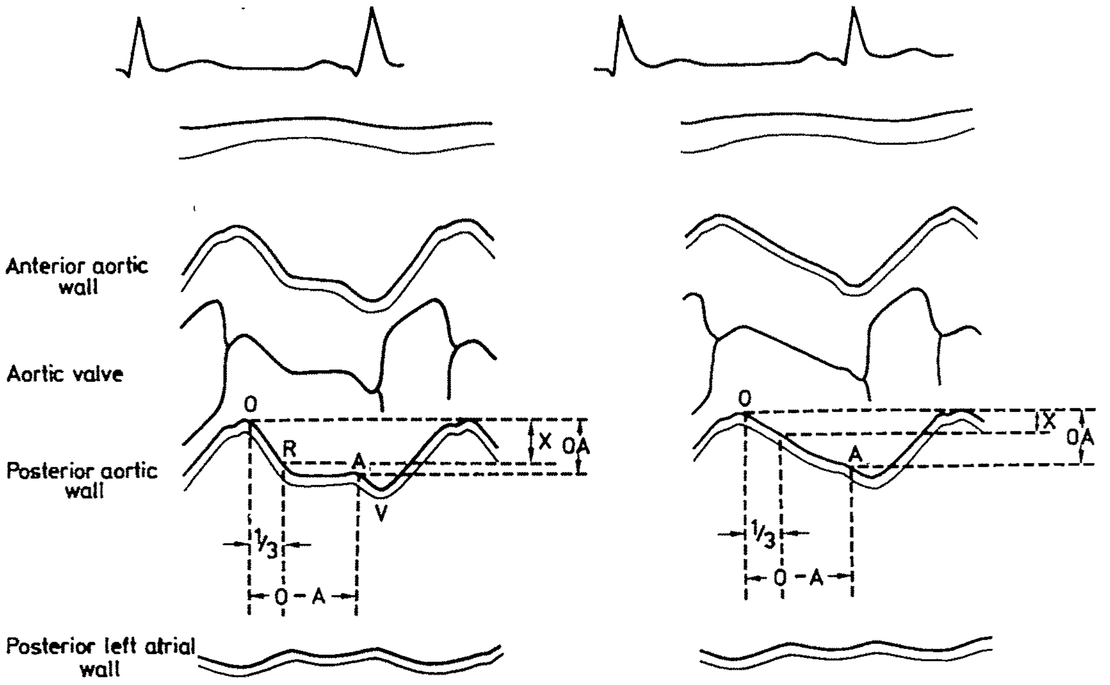

Fig 1 *The atrial emptying index represents the ratio (X/OA) between aortic root motion during first third (O-R) of the passive left ventricular filling period and that of the whole period (O-A). The normal situation is shown in the left part of the figure The right part of the figure shows a decreased X/OA.*

of the aortic component (A2) of the phonocardiogram recorded on the M mode tracing of the mitral valve to the mitral valve opening.

We used the mean value for five beats measured on the apexcardiograms. From simultaneous recordings of the apexcardiogram, phonocardiogram, and electrocardiographic lead II we measured the rapid filling wave and adjusted for the total amplitude of the apexcardiogram (RFW/H).[17] The A2-O interval was measured as the time between the aortic component of the second heart sound and the O point of the apexcardiogram. The pulmonary component (P2) was calculated as the percentage of the aortic component (A2) of the second heart sound (P2/A2%). The third and fourth heart sound amplitudes were measured and were expressed as percentages of the amplitude of the first heart sound (3rd% and 4th%).

Early diastolic filling period, or the distance between mitral valve opening and the O point of the apexcardiogram (Mo-O), was measured by subtracting A2-Mo from the A2-O interval. Because the A2-Mo and A2-O intervals were related to heart rate, we used the regression equations of A2-Mo and A2-O on heart rate in control group A to adjust for heart rate. The heart rate adjusted intervals were called A2-Mo% and A2-O%.

STATISTICAL METHODS

Possible relations were tested with Pitman's non-parametric permutation test, which, when applied for two groups is the same as Fisher's exact test. Pearson's correlation coefficients were calculated for some of the analyses.

We used multiple linear regression technique for multivariate analysis. P values < 0.05 were regarded as statistically significant.

Results

Echocardiographic or phonocardiographic findings did not indicate haemodynamically important valve lesions in any of the men. In two of the men with dyspnoea grade 2 we found left ventricular aneurysms on cross sectional echocardiography. They were not excluded because left ventricular dimension and thickness (the only variables that could have been misinterpreted due to the aneurysms) were normal.

Table 1 *Heart rate, blood pressure, echocardiographic left ventricular dimensions and mass (mean (SE))*

	Control groups		*Dyspnoeic groups*		
	(A)	*(B)*			*Relation to dyspnoea*
Dyspnoea grade	*0*	*0*	*1–3*	*4*	*grade (0–4)*
Cardiac disease	–	+	+	+	*(n = 87)*
	(n = 14)	*(n = 31)*	*(n = 37)*	*(n = 5)*	*p for trend*
Heart rate (beats/min)	55(2)	58(2)	58(2)	83(6)	0 012
Systolic BP (mm Hg)	147(4)	154(4)	152(4)	145(5)	0 243
Diastolic BP (mm Hg)	83(3)	88(2)	85(2)	91(6)	0 600
Mean arterial BP (mm Hg)	104(3)	110(2)	108(2)	109(4)	0 348
LV dimension (mm)	48 8(1 1)	51·4(1 2)	54 9(1 5)	54 4(2 6)	0 078
Septal thickness (mm)	10·6(0·6)	11 3(0 5)	11·5(0 5)	12 4(1 7)	0 129
Posterior wall thickness (mm)	8·9(0 6)	9 3(0 3)	10 6(0 4)	12·0(0 9)	0 002
LV mass (g)	166(12)	205(12)	243(19)	295(40)	0 012
Relative LV mass (g/m^2 BSA)	87(7)	105(5)	125(9)	147(20)	0 017

BP, blood pressure; BSA, body surface area, LV, left ventricular.

DYSPNOEA VERSUS BLOOD PRESSURE AND LEFT VENTRICULAR MASS

The degree of dyspnoea correlated significantly with left ventricular mass and mass index (table 1). Dyspnoea grade showed a significant relation with posterior wall thickness but not with septal thickness or left ventricular diastolic dimension. Dyspnoea grade was not related to the blood pressure level measured after 45 minutes of supine rest.

DYSPNOEA VERSUS DIASTOLIC TIME INTERVALS

The isovolumic relaxation time adjusted for heart rate (A2-Mo%) tended to be longer (not significantly) in control group B and in the men with mild to moderate dyspnoea than in control group A (table 2). But men with severe dyspnoea had significantly lower A2–Mo% than men with mild to moderate dyspnoea (p =0 02). A2-O% was significantly (p = 0·01) prolonged in men with lower grade dyspnoea than in the control group A. In men with severe dyspnoea the A2-O% was again shorter, although not significantly so.

Table 2 *Diastolic time intervals (mean (SE))*

	Control groups		*Dyspnoeic groups*	
	(A)	*(B)*		
Dyspnoea grade	*0*	*0*	*1–3*	*4*
Cardiac disease	–	+	+	+
	(n = 14)	*(n = 31)*	*(n = 37)*	*(n = 5)*
Heart rate mitral echocardiogram (beats/min)	63(3)	63(3)	60(2)	79(5)
A2-Mo (ms)	69(7)	78(4)	79(5)	45(8)
A2-Mo%	100(10)	113(6)	111(7)	69(11)
Heart rate apex-cardiogram (beats/min)	57(3)	60(3)	60(2)	77(5)
A2-O (ms)	153(6)	159(4)	167(4)	133(8)
A2-O%	100(3)	105(2)	112(2)	104(3)
Mo-O (ms)	89(5)	85(3)	88(6)	93(4)

A2-Mo, time from aortic component of second heart sound to mitral opening, A2-Mo%, A2-Mo as percentage of expected value, A2-O, time from A2 to apexcardiographic O-point; A2-O%, A2-O as percentage of expected value, Mo-O, time from mitral opening to the O-point.

DYSPNOEA COMPARED WITH INDICES OF LEFT VENTRICULAR EARLY FILLING, HEART SOUNDS, ATRIAL SIZE, AND INDICES OF PULMONARY ARTERY PRESSURE

There was a significant relation between dyspnoea and atrial emptying index, rapid filling wave (RFW/H), and the third heart sound (3rd%) (table 3). Dyspnoea was also significantly related to the fourth heart sound (4th%), left atrial diameter, left atrial index (left atrial dimension adjusted for body surface area), pulmonary component of the second heart sound, and the diameter of the right ventricle.

Dyspnoea grade correlated with the absolute amplitudes of the first heart sound (r = −0·25, p = 0·04) and with the third heart sound (r = 0·39, p = 0·003), but not with the absolute amplitude of the fourth heart sound (r = 0·08, NS). The amplitude of the third heart sound was related to the rapid filling wave (RFW/H), both with (3rd%), (r = 0·60, p < 0·0001) and without (r = 0·56, p < 0·0001) adjustment for the amplitude of the first heart sound. The absolute amplitude of the third heart sound was not related to the amplitude of the first heart sound, whereas the absolute fourth heart sound amplitude was (r = 0·28, p = 0·03).

LEFT VENTRICULAR WALL THICKNESS AND MASS COMPARED WITH BLOOD PRESSURE, CLINICAL HISTORY, AND INDICES OF DIASTOLIC LEFT VENTRICULAR FUNCTION

Left ventricular mass index (but not posterior wall thickness) was significantly related with systolic (r = 0·41, p = 0 002), diastolic (r = 0·36, p = 0·005), and mean (r = 0 44, p = 0·0004) arterial blood pres-

Table 3 *Indices of left ventricular distensibility and pulmonary artery pressure (mean (SE))*

	Control groups		*Dyspnoeic groups*		*Relation to dyspnoea grade (0–4) (n = 87) p for trend*
	(A)	*(B)*			
Dyspnoea grade	*0*	*0*	*1–3*	*4*	
Cardiac disease	–	+	+	+	
	(n = 14)	*(n = 31)*	*(n = 37)*	*(n = 5)*	
Left ventricular:					
Peak dD/dt (cm/s)	9·4(0·7)	9·5(0·5)	9·6(0·5)	8·1(0·7)	0·154
Time to peak dD/dt (ms)	185(11)	162(10)	167(10)	136(13)	0·493
Posterior wall:					
Peak − dD/dt (cm/s)	6·8(0·5)	6·3(0·5)	7·8(0·4)	6·4(0·8)	0·909
Time to peak dD/dt (ms)	183(12)	151(14)	149(8)	134(14)	0·404
Atrial emptying index	0·88(0·04)	0·85(0·04)	0·79(0·04)	0·54(0·15)	0·025
RFW/H (%)	7·5(0·7)	8·1(0·9)	6·1(0·7)	15·1(4·3)	0·036
3rd%	1(1)	1(0)	4(1)	39(25)	0·008
4th%	12(3)	10(1)	15(3)	47(31)	0·010
Left atrial dimension (mm)	39·8(1·7)	43·3(1·1)	45·9(1·0)	52·4(2·9)	0·001
Relative left atrial dimension (mm/m² BSA)	21·3(1·0)	22·3(0·6)	23·3(0·5)	26·4(1·3)	0·024
P2/A2 (%)	10(7)	28(8)	32(8)	97(62)	0·032
Right ventricular dimension (mm)	21·6(2·8)	20·3(1·4)	20·4(1·5)	32·3(3·1)	0·022

BSA, body surface area; dD/dt, rate of change of dimension (during left ventricular filling period); P2/A2, pulmonary component as percentage of aortic component of second heart sound; RWF/H, amplitude of rapid filling wave as percentage of total height of apexcardiogram; 3rd%, third heart sound amplitude as percentage of first sound amplitude; 4th%, fourth heart sound amplitude as percentage of first sound amplitude.

sure and with a history of treated hypertension (r = 0·39, p = 0·003).

Left ventricular posterior wall thickness (r = 0·34, p = 0·005) and left ventricular mass index (r = 0·38, p = 0·007) were related to a clinical history of myocardial infarction. Posterior wall thickness was also related to a history of angina pectoris (r = 0·31, p < 0·01), whereas mass index was not (r = 0·17, p = 0·205).

The left atrial dimension correlated with posterior wall thickness (r = 0·44, p = 0·0002) and even better with left ventricular mass index (r = 0·57, p = 0·0001) as did the left atrial index (r = 0·48, p = 0·0002). Also the pulmonary component (P2/A2%) (r = 0·32, p = 0·027) correlated positively with left ventricular mass index, while there was an inverse correlation between the latter and atrial emptying index (r = − 0·36, p = 0·013). Neither diastolic time intervals, nor the third or fourth heart sounds, correlated significantly with mass.

MULTIVARIATE ANALYSES OF THE RELATION BETWEEN DYSPNOEA AND FUNCTIONAL VARIABLES

Associations between non-invasive measurements and clinical variables with dyspnoea were evaluated by multivariate analyses.

The first step was to examine the relation between dyspnoea grade and a history of angina pectoris, myocardial infarction, tobacco consumption, treatment for hypertension, blood pressure, heart size and pulmonary congestion at *x* ray examination, atrial fibrillation and Q waves in the electrocardiogram, and vital capacity. Angina pectoris, pulmonary con-

Table 4 *The results from univariate and multivariate analysis of the contribution to the explanation of dyspnoea grade variance*

	Univariate analysis			*Multivariate analysis*		
	r	*p*	*Proportion of explained variance*	*Additional proportion of explained variance*	*p*	*Cumulative proportion of explained variance*
Angina pectoris	0·51	<0·0001	0·26	0·30*	0·0001	0·30
Pulmonary congestion	0·46	0·0003	0·21	0·15	0·0001	0·45
Electrocardiographic Q waves	0·39	0·0012	0·15	0·06	0·0017	0·51
Left atrium (mm)	0·36	0·0010	0·13	0·04	0·0141	0·55
Atrial emptying index	−0·26	0·0252	0·07	0·02	0·0638	0·57

*The discrepancy to univariate analysis is the result of two missing values in the multivariate analysis.

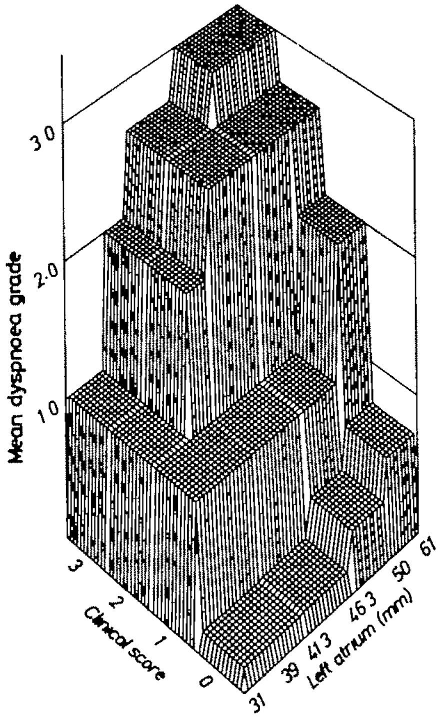

Fig 2 *Mean dyspnoea grade in groups of men according to left atrial size (quantiles) and clinical involvement. The latter was indicated by the presence of Q waves in the electrocardiogram, pulmonary congestion on x ray, and a history of angina pectoris (one point for each). The points were summed up in a clinical score shown along the left horizontal axis.*

gestion, and Q waves accounted for 47% of the variation in grade of dyspnoea. They were the only factors that contributed to the explanation when the other variables were accounted for.

In a second step the contributions of posterior wall thickness, left ventricular mass, and the variables of diastolic function were examined. These variables accounted for 16% of the variation in the grade of dyspnoea. Left atrial size and atrial emptying index were the only independent significant variables.

In the third and last step the three independent significant factors from step 1 and the two from step 2 were introduced into a multivariate analysis. The left half of table 4 shows the results of the univariate analysis. The variables are listed in order of univariate correlation with dyspnoea grade. The right half of table 4 shows the contribution of each variable and the cumulative explanation of dyspnoea grade variance. In order of significance the factors contributing to variance were angina, pulmonary congestion, Q waves, left atrium, and the atrial emptying index. The atrial emptying index did not remain significant when the other variables were taken into account. The five variables could explain 57% of the variation of dyspnoea grade.

In figure 2 the presence of angina, pulmonary congestion, and Q waves in the electrocardiogram scored one point each. Figure 2 shows the mean dyspnoea grade in groups of men according to their clinical score and atrial diameter.

EARLY DEVIATIONS FROM NORMAL

To evaluate whether any diastolic variable is associated with early heart failure, we tested the differences in mean values between mild to moderate dyspnoea (grade 1–3 group) and the control group A. As already stated, the A2-O% was prolonged ($p<0\cdot02$), indicating a prolonged relaxation/early filling period in mild to moderate dyspnoea. Also the posterior wall thickness was significantly increased ($p<0\cdot03$) as was the sum of septal and posterior wall thicknesses ($p<0\cdot02$), while septal thickness alone was not significantly increased. The left atrial dimension was increased ($p<0\cdot003$). On the other hand, indices of severe heart failure, such as an increased pulmonary component, the third heart sound, rapid filling wave, and right ventricular dimension, were not significantly different in men with dyspnoea grade 1–3 and the group A controls.

A COMPARISON OF DIASTOLIC AND SYSTOLIC FUNCTION

Since systolic dysfunction may explain signs of increased filling pressures, the relation between the grade of dyspnoea and left atrial dimension was evaluated by multiple regression analyses, taking the effect of fractional shortening and end systolic dimension into account. Significant contributions to the explanation of dyspnoea grade were still obtained from left atrial dimension when considering: (*a*) left atrial dimension ($p = 0\cdot01$) and fractional shortening ($p = 0\cdot002$); (*b*) left atrial dimension ($p = 0\cdot02$) and end systolic dimension ($p = 0\cdot02$); (*c*) left atrial dimension ($p = 0\cdot01$), fractional shortening ($p < 0\cdot04$), and end systolic dimension (p = NS).

Discussion

In the present study cardiac dyspnoea was related to left ventricular hypertrophy and to diastolic abnormalities, some of which were primary and others which may have been secondary to systolic dysfunction. Diastolic and systolic function of the heart are closely related, both on the atrial[18] and the ventricular[19] levels. Diastolic abnormalities may cause congestive heart failure in the absence of systolic dysfunction.[8 9] Nevertheless, diastolic and systolic function are often abnormal simultaneously,[19] and both may increase filling pressures. It was therefore necessary to take the degree of systolic impairment into account when determining the importance of diastolic abnormalities to the degree of cardiac dyspnoea.

LEFT VENTRICULAR HYPERTROPHY

In the Framingham study the prevalence of echocardiographic left ventricular hypertrophy was 23·7% among men who were about 70 years old.[20] In the present study an increase in left ventricular wall thickness was responsible for the increase in left ventricular mass in men with dyspnoea. An increased left ventricular dimension also contributed to the increasing left ventricular mass, but left ventricular dimension per se was not significantly related to dyspnoea grade. Left ventricular mass was significantly correlated with blood pressure, indicating that hypertension contributed to congestive heart failure in the present study group, as it did in the Framingham study.[21] In coronary heart disease there is left ventricular hypertrophy caused by an increase in the thickness of non-infarcted areas to compensate for myocardial loss elsewhere.[22] It has been suggested that increased left ventricular wall thickness in coronary or hypertensive heart disease causes filling problems,[23] and that diastolic function abnormalities are related to wall thickness.[24] Nevertheless, in athletes with a corresponding degree of hypertrophy diastolic variables were normal.[24 25] It has therefore been suggested that abnormalities of diastolic function, as seen in pathological hypertrophy, are partly the result of factors other than the cardiac hypertrophic process as such.[25] Age is such a factor. Age influences the diastolic properties of the heart,[26-28] and may have a role in the development of symptoms of heart failure in the elderly.[29] This factor cannot have influenced our results because all the men we studied were the same age.

LEFT VENTRICULAR RELAXATION AND EARLY FILLING PROPERTIES

In addition to signs of left ventricular hypertrophy, men with mild to moderate dyspnoea had an increased A2-O%, which accords with previous results indicating that prolongation of the A2-O interval is an early indication of myocardial dysfunction.[1 2] A prolonged A2-O interval or isovolumic relaxation period may be caused by left ventricular hypertrophy or incoordinate left ventricular relaxation secondary to coronary artery disease, although the duration of diastolic time intervals is not always a valid reflection of left ventricular relaxation when there is pressure or volume overload.[30] Left ventricular relaxation probably extends beyond the isovolumic phase and contributes to left ventricular filling,[30] and its duration may therefore be approximated by the A2-O interval, which may be regarded as a measure of the time required for left ventricular pressure to reach its nadir.[31] We expected that, after adjustment for heart rate, the A2-Mo and A2-O intervals would increase with increasing degree of dyspnoea because of impaired left ventricular relaxation. However, in the group with severe dyspnoea an increased atrial pressure was likely to have caused early opening of the mitral leaflets[31] and a short left ventricular filling time.[32] If so, a further decrease in A2-Mo% and A2-O% would be expected in the most dyspnoeic group. This turned out to be the case.

Dyspnoea grade was related to the relative amplitude of the third heart sound (3rd%) and to the rapid filling wave which were grossly abnormal in severe heart failure. The third heart sound is an early diastolic event of obscure pathogenesis,[33] which, when heard as a gallop sound in myocardial infarction, is related to raised pulmonary artery pressure and associated with a poor prognosis.[34] In the present study, and others,[26] a relation was found between the third sound and the rapid filling wave amplitudes. We used the same equipment to record the third sound in all men. The influence of age[26 27] as a confounding factor could be disregarded, but not inherent differences in thoracic auditory transmission. Therefore, the first heart sound was used as a reference. The first heart sound could be influenced by contractile performance of the left ventricle—that is the systolic performance. This hypothesis was supported by a significant inverse correlation between the first heart sound and the dyspnoea grade. The amplitude of the third heart sound was not only correlated with the dyspnoea grade but also did not correlate significantly with the first heart sound. Moreover, an increase of the third heart sound is not likely to have been caused by good thoracic transmission, since the men with the most severe dyspnoea had a larger body mass index than the control group. These findings indicate that the relation between dyspnoea grade and the third heart sound was not caused by bias.

Among men with severe dyspnoea (grade 4) there was a reduced atrial emptying index, and a tendency (trend not significant) towards a lower left ventricular filling rate as well as to a slower rate of posterior wall thinning.

In the absence of mitral stenosis a reduced atrial emptying index (indicative of a reduced rate of early diastolic filling) is an expression of impaired left ventricular filling.[8 16] Although the aortic root motion may be influenced by several factors, it seems to be governed mainly by the rate of change in left atrial volume.[16] Rapid early diastolic wall thinning is likely to be a manifestation of relaxation and is a major determinant of left ventricular filling.[35] A reduced diastolic filling rate has been reported in homogeneous groups of patients with coronary[16,36] and hypertensive[23,24] heart disease, but other studies, like ours, reported no significant difference between controls and patients with left ventricular disease,[37] angina pectoris,[38] or coronary disease with no systolic dysfunction.[39] Atrial pressure may influence the atrial emptying index, as well as the peak change in left ventricular dimension and wall thinning,[40,41] which are also indices directly associated with myocardial contractility.[19]

LEFT VENTRICULAR DISTENSIBILITY AND ATRIAL AND PULMONARY ARTERY PRESSURES

Left ventricular distensibility, often used interchangeably with the term compliance, is the change in volume relative to a change in pressure,[42] a relation that we could not measure non-invasively. Indirect non-invasive tests of distensibility are based on the relative power of the left atrium needed to force the blood into the left ventricle.[4,17] However, with severe left ventricular failure, not only atrial failure, but also the raised filling pressure may cause a "paradoxical" decrease of echocardiographic (Caidahl *et al*, unpublished), Doppler,[43] and apexcardiographic[44] signs of the previously increased atrial contribution to left ventricular filling. This phenomenon complicates the non-invasive study of left ventricular distensibility in heart failure. In this study dyspnoea grade was related to an increased fourth heart sound relative to the first heart sound. We did not feel confident in drawing any conclusions from this fourth/first heart sound ratio, however, because the amplitude of the fourth heart sound in itself did not correlate with dyspnoea grade.

The left atrial dimension may also be regarded as an indirect index of distensibility of the left ventricle,[45] and it does not have the drawbacks mentioned above. When left ventricular distensibility is impaired the atrial contribution to left ventricular filling is augmented[46] and the atrium becomes enlarged. A vigorous atrial contraction may enable the left ventricle to be filled despite an increased end diastolic pressure, and this permits pulmonary capillary pressure to remain at a low level.[47] Finally, with atrial failure, the pulmonary capillary pressure will increase and dyspnoea will ensue or be aggravated.

Systolic dysfunction can also raise filling pressure. The relative influence of diastolic and systolic dysfunction on atrial distension must therefore be considered. In multivariate analyses the left atrial dimension contributed significantly to the explanation of cardiac dyspnoea even when the importance of fractional shortening and end systolic dimension were taken into account. This indicates that the left atrial distension may be caused by a raised filling pressure secondary to diastolic dysfunction.

The grade of dyspnoea was related to the atrial dimension, and the latter was also correlated with left ventricular wall thickness. There was a significant increase of left atrial size in mild to moderate grade dyspnoea and the dyspnoea grade increased with left atrial size. However, atrial enlargement was accompanied by an increase in the pulmonary component calculated as a percentage of the aortic component of the second heart sound and an enlarged right ventricular dimension only in the most severe dyspnoea grade reflecting a raised pulmonary artery pressure in this group.

CLINICAL IMPLICATIONS

Diastolic left ventricular abnormalities were more common the more advanced the degree of dyspnoea in the present study, supporting the concept that left ventricular diastolic function is important in the generation of dyspnoea in congestive heart failure. Concomitant systolic dysfunction may be the primary event in many cases, causing raised filling pressures. Nevertheless, multivariate analyses showed that diastolic impairment causing an enlarged left atrium made a significant independent contribution to cardiac dyspnoea when the contribution from systolic function was taken into account. Increased left atrial dimension, myocardial hypertrophy, and prolonged A2-O% in mild to moderate dyspnoea also support this concept, since we have already found[11] that dyspnoea grade 1–3 was associated with normal fractional shortening. As a consequence, not only in individuals with hypertrophic cardiomyopathy,[48] but also in patients with heart failure, therapeutic measures[6,49] aimed at improving diastolic function may be useful. Drug trials are required to establish the potential pathophysiological and therapeutic value of correcting diastolic abnormalities in congestive heart failure.

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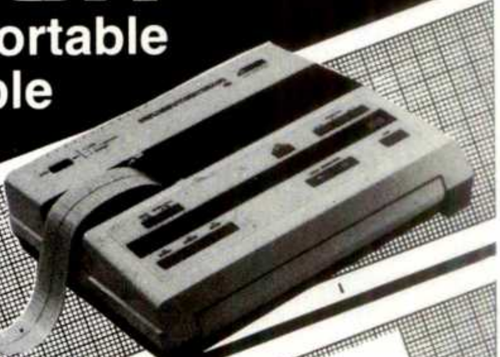

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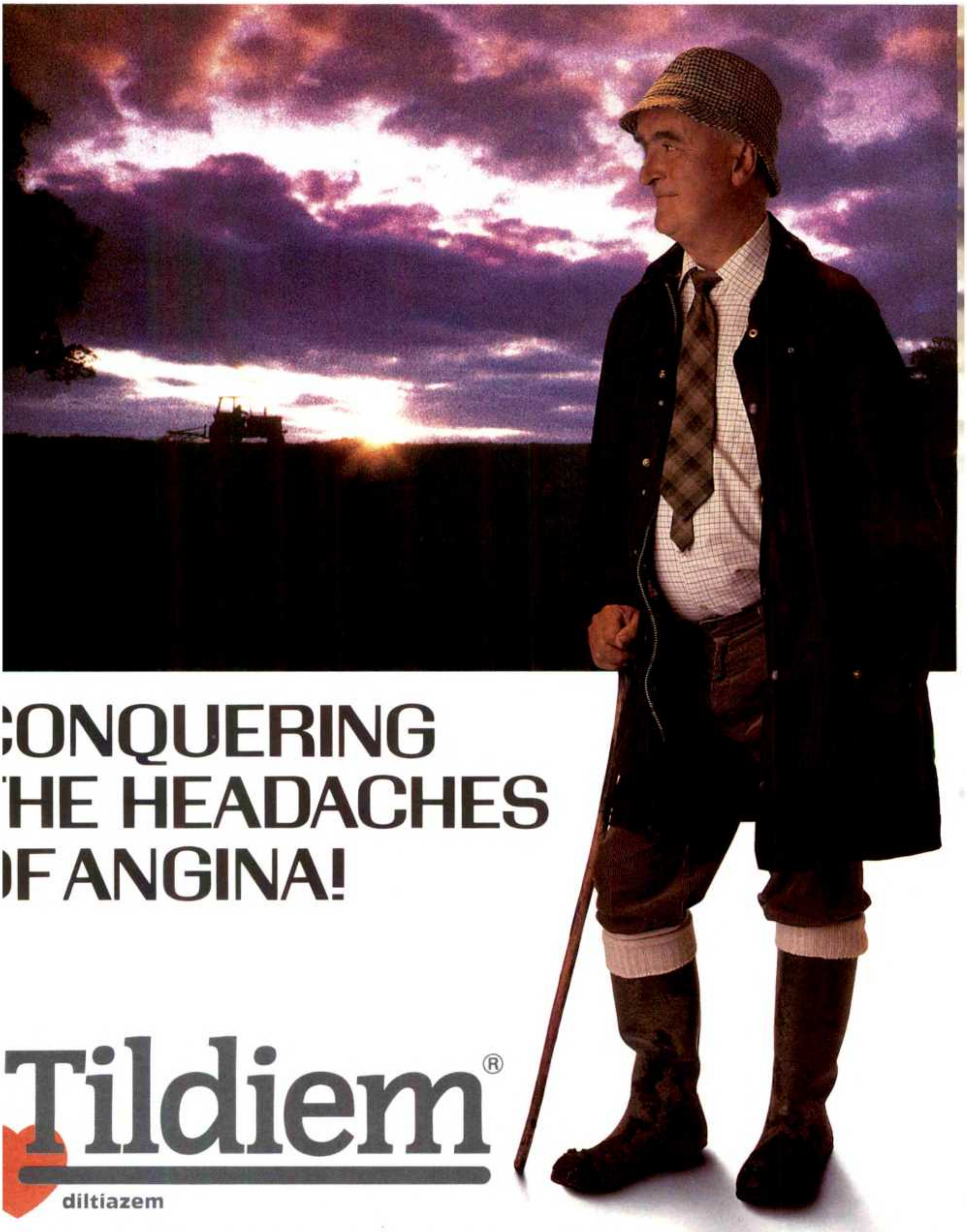

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Br Heart J 1988;59:339–51

The cross sectional anatomy of ventricular septal defects: a reappraisal

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SUMMARY The cross sectional echocardiographic description of holes in the ventricular septum has been unsatisfactory, chiefly because there are so many classifications of this defect. The accurate description of the anatomy of individual defects, from cross sectional images, is more important than attempts to fit them into a preconceived classification. One hundred specimens of hearts with a ventricular septal defect were reviewed to identify those features that are of value in the interpretation of cross sectional images. Three groups of defect were identified: those which abutted the central fibrous body, those with a margin partly formed by an area of fibrous continuity between the leaflets of the aortic and pulmonary valves, and those with entirely muscular margins. Each group had features that were readily discernible in cross section. Other features of the defects seen in the cross sectional images identified defects that opened between the two ventricular inlets, defects that opened between the two subarterial outlets, and those that extended solely into the trabecular septum. The criteria for describing the anatomy of defects were established in hearts with normal connections, but they were found to be equally applicable in hearts with discordant atrioventricular connection, discordant ventriculoarterial connection, common arterial trunk, and double outlet from the morphologically right ventricle. Cross sectional imaging, by echocardiography and potentially by other techniques, provided a uniquely detailed and precise description of the morphology of ventricular septal defects.

The understanding of the morphology of holes between the ventricles has been complicated by the plethora of existing and proposed schemes of classification. Several cross sectional echocardiographic studies of the anatomy of ventricular septal defects have been published.[1-3] In each, the authors interpreted the echocardiographic images by reference to an established classification. Despite these reports, or perhaps because of them, uncertainties remain about the interpretation of cross sectional images of ventricular septal defects. We have, therefore, restudied the morbid anatomy of ventricular septal defects to identify those morphological features that are important in the interpretation of cross sectional images.

Patients and method

We examined a representative series of specimens with a ventricular septal defect from the heart museum of the Children's Hospital of Pittsburgh. Hearts with an atrioventricular septal defect, pulmonary or aortic atresia, or a univentricular atrioventricular connection were excluded. The margins of each defect were carefully inspected to identify the features that were amenable to cross sectional imaging. Where necessary, hearts were sectioned to simulate echocardiographic planes and to clarify the cross sectional appearances. After the anatomical study, cross sectional echocardiograms from patients with ventricular septal defects studied at the Children's Hospital, Pittsburgh were selected to illustrate some of the important morphological features.

Results

In all, 100 hearts were examined (table). Fifty two had a ventricular septal defect in the setting of usual (concordant) chamber connections. In addition, we

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Table *A list of hearts examined with the category of ventricular septal defect*

Connection	*No*
Normal connections:	
Perimembranous	42
Muscular	8
Doubly committed and juxta-arterial	2
Complete transposition:	
Perimembranous	4
Muscular	9
Doubly committed and juxta-arterial	1
Congenitally corrected transposition:	
Perimembranous	2
Doubly committed and juxta-arterial	1
Both doubly committed and perimembranous	1
Double outlet of the right ventricle:	
Perimembranous	14
Muscular	1
Doubly committed and juxta-arterial	4
Common arterial trunk	
Perimembranous	8
Muscular right ventricular margin	3

examined 18 hearts with ventricular septal defect and a discordant ventriculoarterial connection—14 of these had a concordant atrioventricular connection and four a discordant atrioventricular connection. A common arterial trunk was present in 11 hearts, all with a concordant atrioventricular connection. A final group of 19 hearts was studied with double outlet from the morphologically right ventricle, again in the setting of a concordant atrioventricular connection. Some of the hearts in this series have been described in previous studies.[4-6]

HEARTS WITH CONCORDANT ATRIOVENTRICULAR AND VENTRICULOARTERIAL CONNECTIONS

Borders of the defect: holes abutting the central fibrous body

In hearts with otherwise normal anatomy, the central fibrous body could be identified as the area of continuity between the tricuspid, aortic, and mitral valves. When a hole in the septum abuts the central fibrous body, it is also, therefore, immediately adjacent to the fibrous structures supporting the leaflets of the aortic valve (fig 1a). In that sense, it is "subaortic".[2] To an extent, this is a confusing term. Often, there is a considerable length of fibrous tissue between the edge of the defect and the origin of the leaflets of the aortic valve (fig 1b). Furthermore, many observers would consider a defect to be more

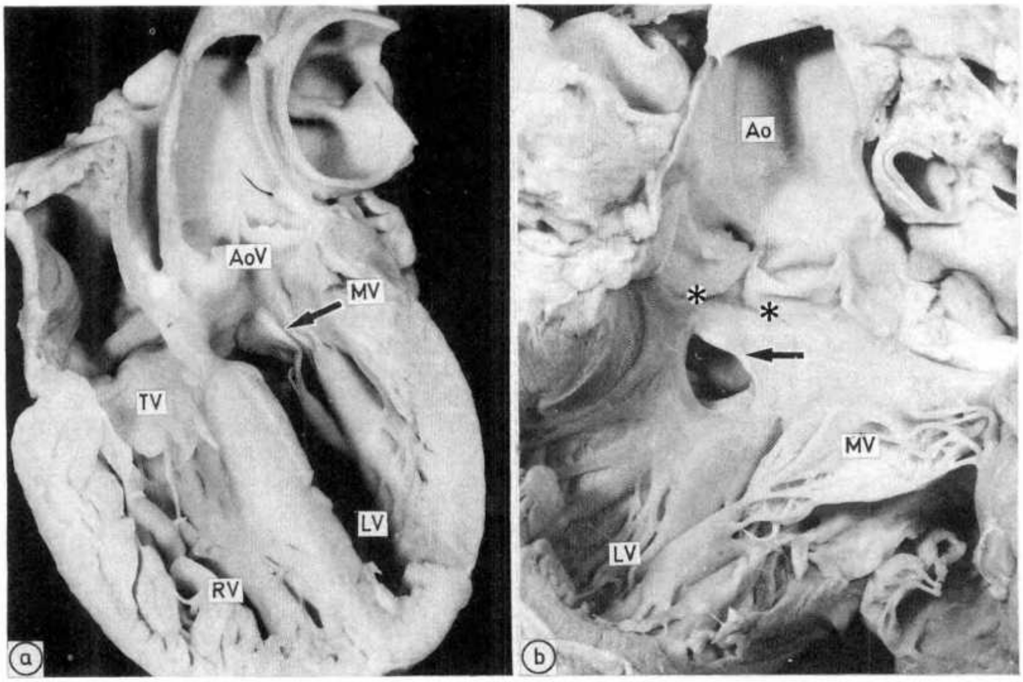

Fig 1 *(a) This simulated four chamber cut, incorporating the aortic (Ao) root, shows how the cardinal feature of the defect we choose to call perimembranous is fibrous continuity between the tricuspid (TV), aortic (AoV), and mitral (MV) valves in the roof of the defect. In some circumstances, as shown in a view from the left ventricle (b), a substantial ridge of fibrous tissue (arrowed) may hang below the attachments of the leaflets of the aortic valve (asterisks). RV, right ventricle.*

obviously "subaortic" when there is overriding of the valve orifice as, for example, in the tetralogy of Fallot. There is, none the less, a need to describe specifically those defects bordered superiorly by the fibrous tissue supporting the aortic root. A major component of this tissue is the atrioventricular membranous septum and the defects are disposed around this fibrous partition. For this reason, and despite the reservations expressed by others, we continue to describe this group of defects as perimembranous.[7]

Perimembranous defects were the most common in this series. The openings of some of them extended into the inlet, outlet, or trabecular zones of the ventricles. Small defects could be judged morphologically to be opening into the right ventricular inlet or outlet by virtue of their relation to the medial papillary muscle. Defects above the papillary muscle have been termed "outlet", and those beneath it "inlet", while trabecular extension is indicated by insertion of the papillary muscles at the apical margin of the defect.[7] This morphological distinction was difficult to make in the hearts in which the medial papillary muscle was multiple or ill defined. Furthermore, this relation seemed unlikely to be identified by cross sectional imaging. Thus for imaging purposes we considered it inappropriate to use the terms "inlet", "outlet", and "trabecular" for the description of *small* perimembranous defects. Large perimembranous defects extending posteriorly to open into the right ventricular inlet formed a well defined group, as did those large defects that extended anteriorly to open into the subpulmonary right ventricular outflow tract. In contrast, large perimembranous "trabecular" defects did not form a distinct group. Indeed, they had no morphological features that distinguished them from perimembranous defects extending to open into both the outlet and inlet of the right ventricle. This group was, therefore, described as "confluent".

Holes bordered by fibrous continuity between the leaflet of the aortic and pulmonary valves

We identified a further discrete group of defects in which at one margin there was direct fibrous continuity between the leaflets of the aortic and pulmonary valves (fig 2). Such defects always opened between the two subarterial outlets. They involved an abnormality of septation of this area, as do all outlet defects. These defects have previously been called "supracristal". Our preference is to describe them as doubly

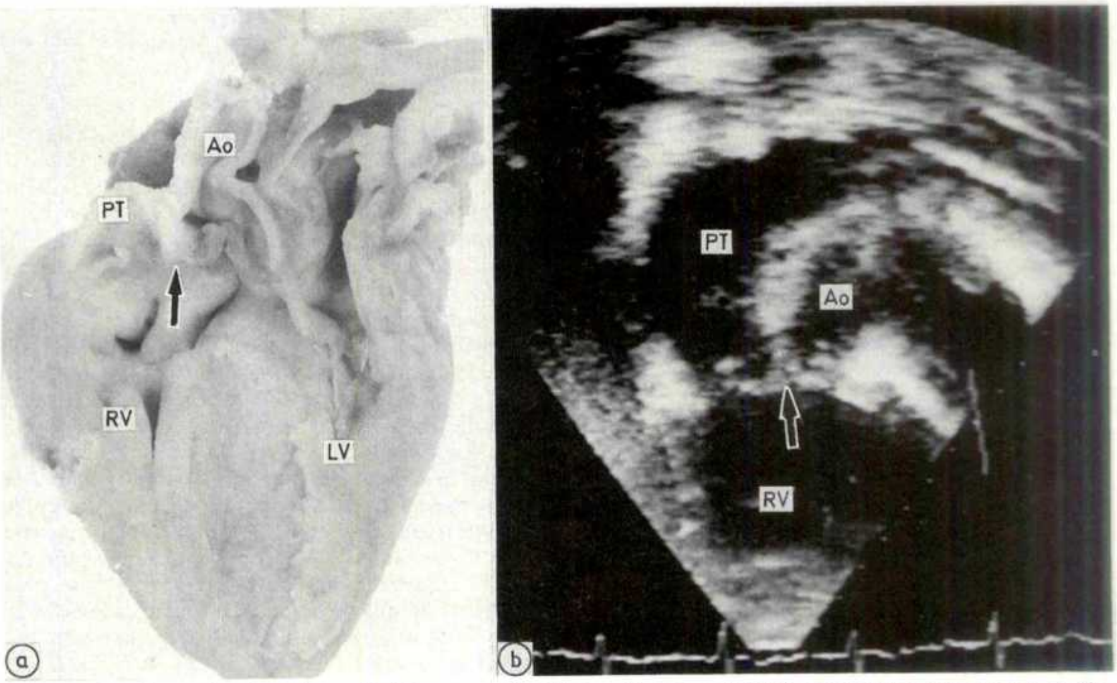

Fig 2 *These illustrations show the cardinal features of the defect we choose to call doubly committed and juxta-arterial. The anatomical specimen is sectioned in a simulated parasternal long axis plane. The defect is roofed by fibrous continuity between the arterial valves (arrowed). The echocardiogram is an oblique subcostal cut and shows both great arteries (pulmonary trunk (PT) and aorta (Ao)) apparently above the right ventricle (RV). There is clearly fibrous continuity between the arterial valves (arrowed). LV, left ventricle.*

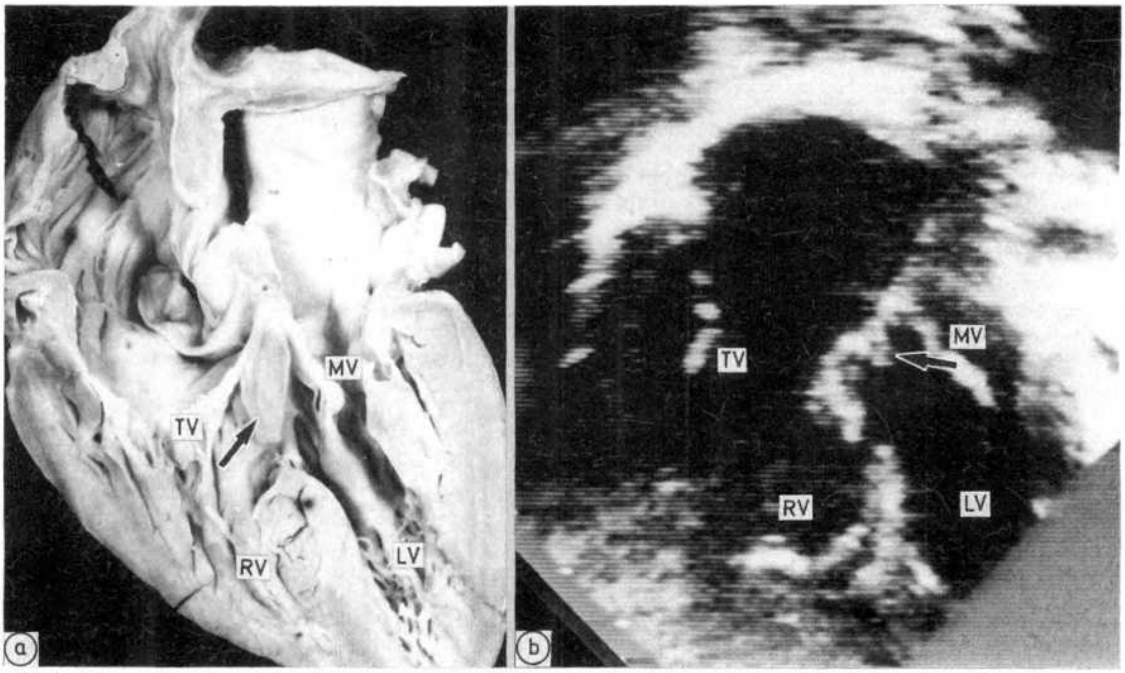

Fig 3 *These figures show defects that are not perimembranous opening between the ventricular inlets. A bar of muscle separates the defect from the area of continuity between the tricuspid (TV) and mitral (MV) valves (arrowed). The offsetting of the insertion of the two atrioventricular valves to the septum is clearly seen in both cases. See legends to figs 1 and 2 for abbreviations.*

committed and juxta-arterial.[7,8] Occasionally a fibrous raphe was present between the two arterial valves. In cross section the leaflets of the valves usually appeared to be at the same level, but careful examination of some of these hearts showed that, for part of the extent of the defect, the valves were offset. The tissue between the leaflets was composed of the arterial wall of a sinus of Valsalva. At some point along the defect, however, the leaflets were always found at the same level, albeit over only a very small area.

Holes with entirely muscular margins

All ventricular septal defects which were not perimembranous and were not doubly committed and juxta-arterial had a margin that was entirely muscular (fig 3). Such defects could be further described according to their position within the muscular septum and their relation to the arterial valves.

Description of the position of holes in the ventricular septum: defects opening between the ventricular inlets

The "inlet" septum, the septum that separates the inlet of the right ventricle from the inlet of the left ventricle, can only be identified in a single plane of the heart. This passes in the long axis posteriorly through the crux of the heart and is usually called the four chamber plane.[9] It follows that a defect which opens between the inlets of both ventricles has to extend into this plane. Anteriorly to the four chamber plane the aortic valve is "wedged" between the two atrioventricular valves and, so, here the septum lies between the inlet of the right ventricle and the outlet of the left ventricle. The term "inlet defect" has been used to describe defects that open into the inlet of the right ventricle posteriorly to the medial papillary muscle but which do not extend far enough posteriorly to reach the crux of the heart.[7] Such defects do not open between the inlets of the two ventricles. They open between the right ventricular inlet and the left ventricular outlet (fig 1a). It must be emphasised that these "inlet" defects are not seen in the four chamber section of the heart. In cross sectional images, it is only those large perimembranous defects that extend to the crux and open between both ventricular inlets which form an identifiable subgroup. In our series perimembranous defects extending to the crux were not common. We judged that in 12 hearts the defect belonged to this category. Continuity between tricuspid and mitral valves formed one margin of these defects and normal

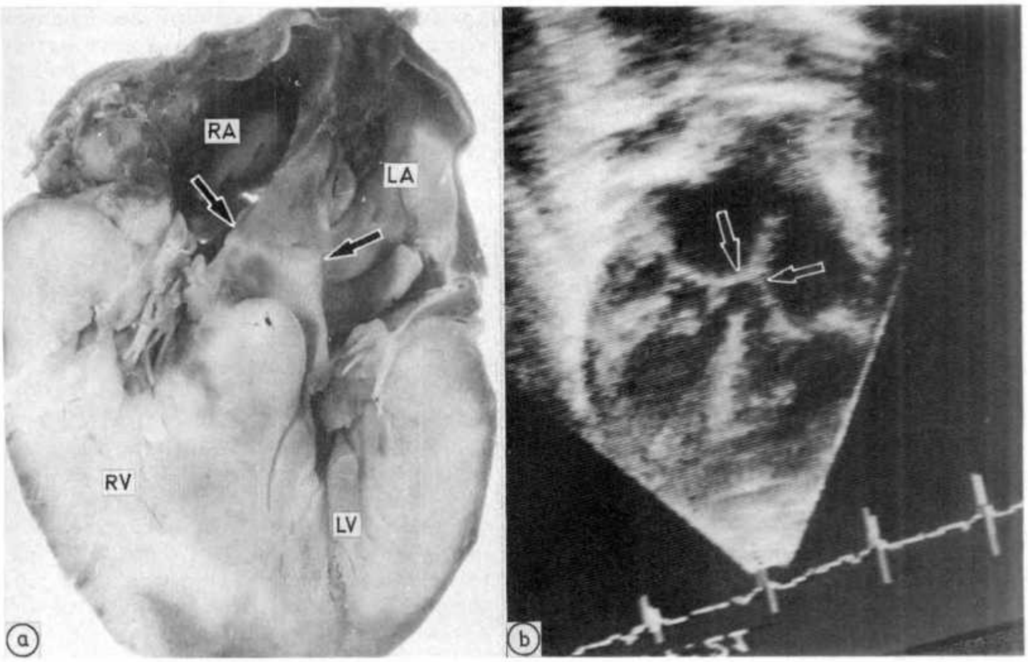

Fig 4 *These sections of a perimembranous defect (not from the same patient) show that the defect extends to the crux, opening between the inlets of the two ventricles. The mitral and tricuspid valves (arrowed) are inserted into the septum at more or less the same level. RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle.*

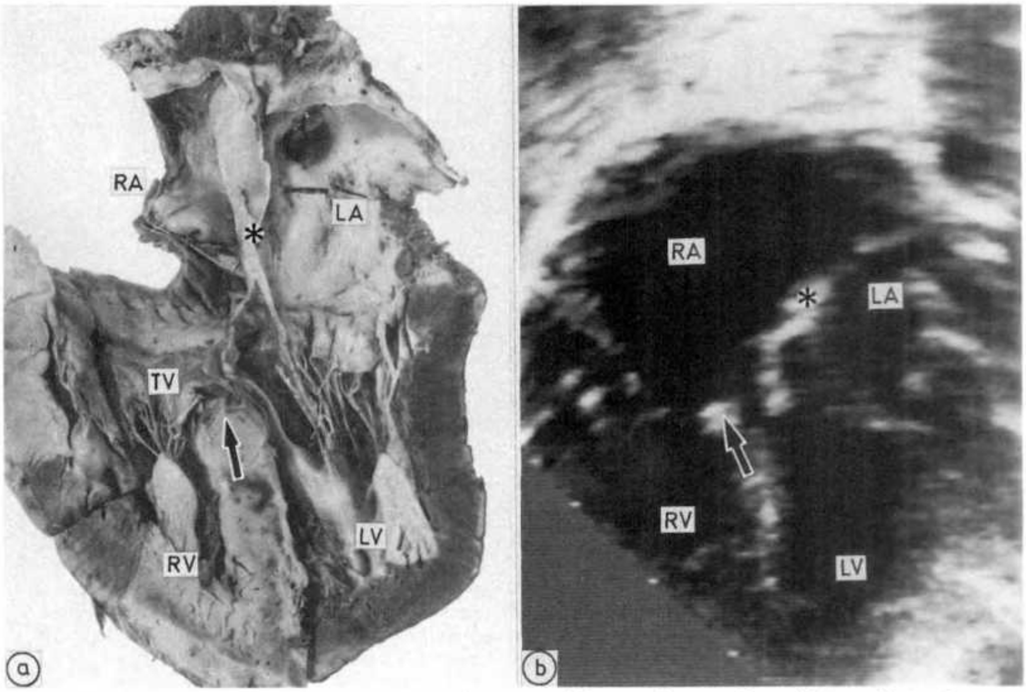

Fig 5 *These sections (not from the same patient) show the malalignment between the atrial (asterisk) and ventricular (arrowed) septal structures that is the hallmark of the inlet defect associated with straddling and overriding of the tricuspid valve (TV). See legends to figs 1 and 2 for abbreviations.*

offsetting of the two atrioventricular valves was absent (fig 4). In one heart in this group, the tricuspid valve overrode and straddled the defect so that the inferoseptal commissure was attached to a papillary muscle within the left ventricle. This was associated with considerable malalignment between the atrial septum and the posterior component of the muscular ventricular septum (fig 5). None of these hearts showed the morphological stigmata of atrioventricular septal defects ("endocardial cushion defects") and none had trileaflet left atrioventricular valves. They are appropriately described as perimembranous defects opening between the inlets of both ventricles—they should not be called "atrioventricular canal defects".

Muscular defects opening between the ventricular inlets also extended into the four chamber plane. They were, in contrast, separated from the atrioventricular valves by a muscle bundle and the normal offsetting of insertion of the valves into the septum was preserved (fig 3). In one heart with a muscular inlet defect, the defect straddled the tricuspid valve.

Holes between the subarterial outlets
The relation between the aortic and pulmonary valves in normal hearts is such that a true "outlet septum", a septum separating the outflows of the left and right ventricles, cannot be identified or else is very small. If, therefore, a ventricular septal defect opens between the outlets of both ventricles, there must be a fundamental difference in the septal morphology of this area. In this series, outlet extension of a perimembranous or muscular defect was characterised by the presence of a true outlet septum, the lower border of which formed one margin of the defect (fig 6). Deviation of this septum anteriorly or posteriorly was associated with overriding by either of the great arteries. Indeed, overriding of an arterial valve was a specific, but not invariable, feature of outlet defects. Subaortic[5] or subpulmonary[6] stenosis was also a feature of some hearts with deviation of the outlet septum.

In the presence of an outlet defect, a coronal section of the heart parallel to the trabecular septum, which passes through the inlet and outlet of the right ventricle, cuts through the aortic root. The aortic valve sits astride the defect, giving the impression that it arises from the right ventricle (fig 6). This feature does not depend on overriding of the aortic valve, the extent of which is difficult to assess in sections parallel to the trabecular septum. Where there is little or no override, however, a more anterior section will demonstrate the ventriculoinfundibular fold separating the ascending aorta from the right

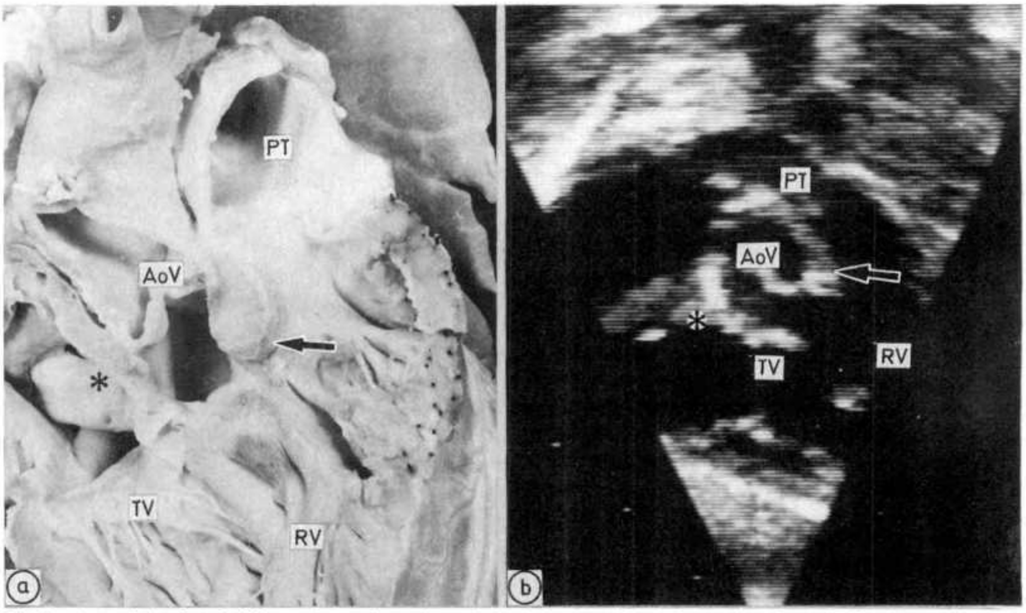

Fig 6 *(a) A simulated oblique subcostal cut through the right ventricle. The aortic valve (AoV) sits astride a ventricular septal defect and appears to arise from the right ventricle. It is separated from the pulmonary valve by a bar of muscle, the outlet septum (arrowed). There is continuity between the tricuspid (TV) and aortic valves (asterisk). This is therefore a perimembranous defect opening between the ventricular outlets and overridden by the aortic valve. (b) Similar appearances are seen in this defect viewed in an equivalent echocardiographic plane. RV, right ventricle; PT, pulmonary trunk.*

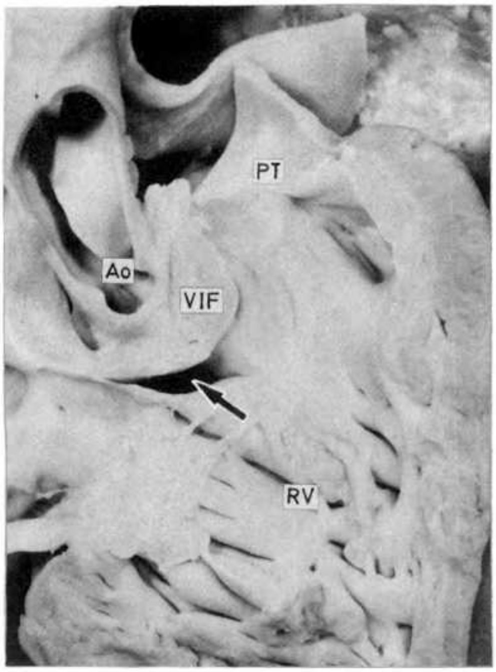

Fig 7 *A simulated oblique subcostal cut in a heart with a perimembranous defect (arrowed) opening between the ventricular outlets with no override. The ventriculoinfundibular fold (VIF) separates the aorta (Ao) from the right ventricle (RV). PT, pulmonary trunk.*

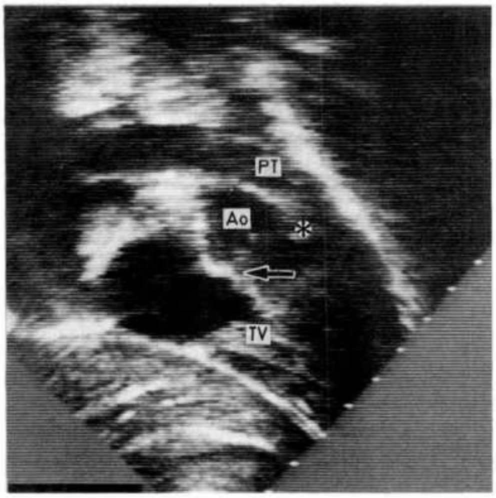

Fig 8 *An oblique subcostal cut in a patient with a defect that was both perimembranous and doubly committed and juxta-arterial. There is fibrous continuity between both the tricuspid (TV) and aortic valves (arrowed) and the aortic and pulmonary valves (asterisk). See legends to earlier figures for abbreviations.*

extremely valuable in the definition of outlet defects. The absence of a muscle bar between the aortic and tricuspid valves indicated that the defect was perimembranous (fig 6). If there was no muscle bar between the aortic and pulmonary valves (that is no outlet septum and therefore an incomplete subpulmonary infundibulum) the defect was doubly committed and juxtaarterial (fig 8). A muscle bar was present at both sites in muscular outlet defects (fig 9) and absent from both sites in defects that were both perimembranous and doubly committed.

HEARTS WITH COMPLETE TRANSPOSITION

The morphological features of defects in hearts with a discordant ventriculoarterial connection were essentially similar to those already described. There was one important difference. The two great arteries usually arise side by side from the heart and therefore there can be a true outlet septum in the absence of a ventricular septal defect. Nevertheless, muscular and perimembranous defects that extend so as to open into the two subarterial outlets were still characterised by demonstration of the outlet septum at one margin. In fact, the most common defect in this group of hearts was a muscular defect at the border between the outlet septum and the trabecular septum (fig 10). This was usually anterior to the septomarginal trabeculation, but occasionally was more posterior, in one case extending to become perimembranous. Deviation of the outlet septum anteriorly into the right ventricular outflow tract or posteriorly into the left ventricular outflow tract was a common accompanying feature.

It is usually the pulmonary valve, not the aortic valve, that is continuous with the central fibrous body in these hearts. Perimembranous defects were, therefore, identified by pulmonary to tricuspid continuity at one margin. In one heart in this group there was a complete muscular infundibulum beneath both arterial valves. Neither arterial valve was attached to the central fibrous body.

HEARTS WITH DISCORDANT ATRIOVENTRICULAR CONNECTION

The morphological features of the defects in these hearts divided them into two groups. In all four hearts studied, the hole opened between the subarterial outlets. In two cases the outlet septum was absent and a muscle bundle separated the defect from the central fibrous body (fig 11a). These defects were doubly committed and juxta-arterial. In the other two hearts, the area of fibrous continuity between the pulmonary and tricuspid valves formed part of the morphologically right ventricular margin of the defects, which were therefore perimembranous (fig 11b). In both cases there was rightward deviation of

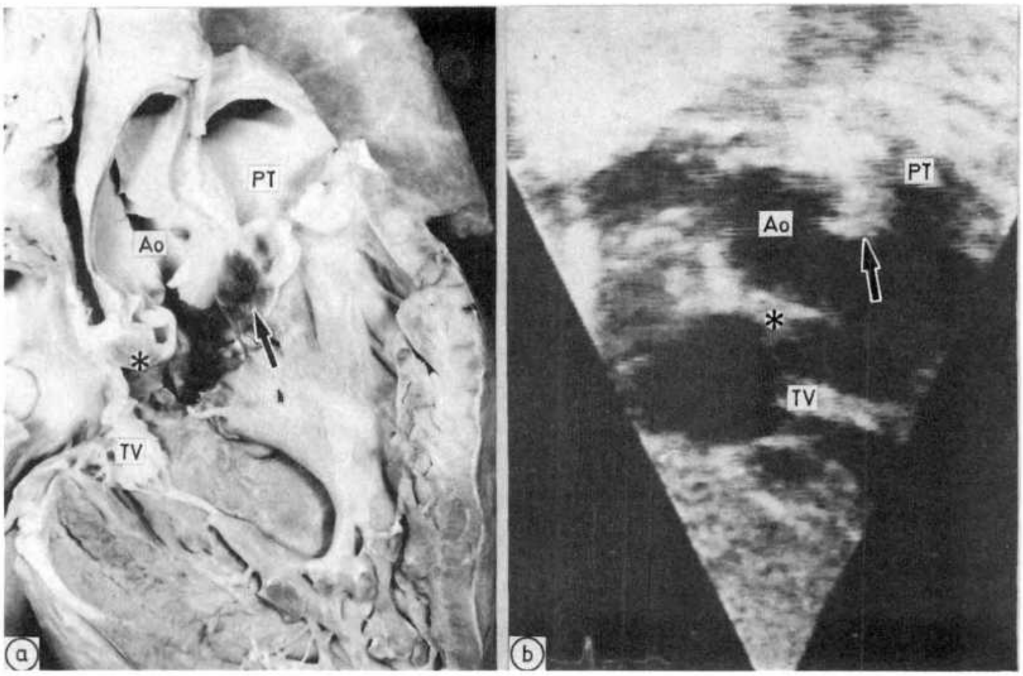

Fig 9 *These two sections (not from the same patient) show a muscular outlet defect. (a) A simulated oblique subcostal cut. (b) An equivalent echocardiographic section. In both cases a muscle bar, the outlet septum (arrowed), separates the arterial valves and another muscle bar (asterisk) separates the aortic and tricuspid valves. See legends to earlier figures for abbreviations.*

the outlet septum and subpulmonary obstruction. The abnormal connection in hearts with a discordant atrioventricular connection did not present any problems in the identification of the borders of the defects in cross section. The important morphological features could be readily described by the criteria already outlined.

HEARTS WITH DOUBLE OUTLET FROM THE RIGHT VENTRICLE

Many of the hearts with this connection had ventricular septal defects opening into both subarterial outlets, the essential morphology of which was not different from that of the other outlet defects that have been described. These hearts were arbitrarily classed as double outlet because the connection of the overriding aortic or pulmonary valve was judged to be greater than 50% to the right ventricle.[10] If an outlet septum was present it was completely within the right ventricle and formed part of the right ventricular margin of the defect. If the central fibrous body also formed part of the right ventricular border, the defect was described as perimembranous. If not, it was described as muscular. Absence of the outlet septum was a feature of doubly committed juxta-arterial defects. In such a case, the fibrous continuity between the arterial valves formed part of the right ventricular margin of the defect. In all these defects, the left ventricular margin was partly made up by the area of fibrous continuity between an arterial valve and the mitral valve. Inferiorly, the crest of the trabecular septum formed the common left and right ventricular border of the defect. In one heart in this group, with a perimembranous defect and an overriding pulmonary valve, the mitral valve straddled the defect. The anterolateral commissure was supported by chordal attachments to the outlet septum.

A subgroup of hearts with double outlet right ventricle had a complete muscular infundibulum beneath both arterial valves. In these hearts, neither arterial valve was continuous with the central fibrous body and, therefore, in no section of the heart was there fibrous continuity between an arterial and atrioventricular valve. A perimembranous defect was identified solely by the demonstration of continuity of the tricuspid and mitral valves at one margin of the defect. With this morphological arrangement, neither great artery was immediately adjacent to a perimembranous defect. In these hearts, the relation of the defect, be it perimembranous or muscular, to either arterial valve was variable and was not predictable from its morphology.

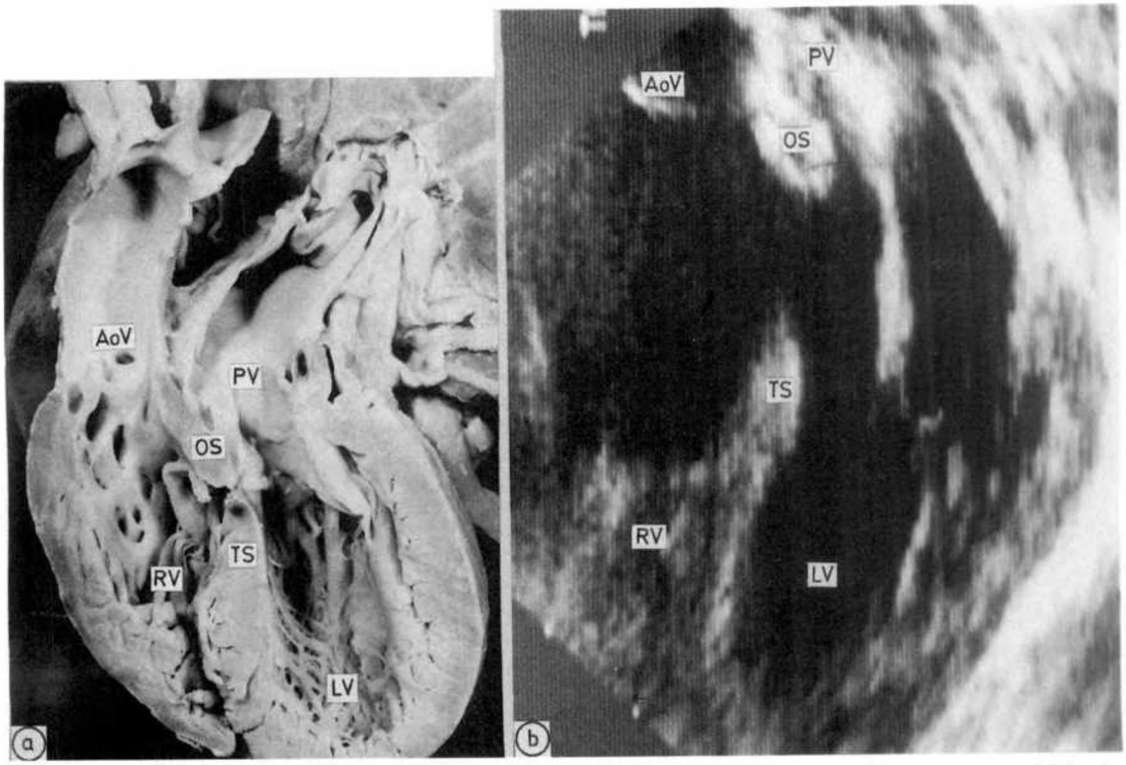

Fig 10 *(a) A simulated parasternal long axis cut in a heart with complete transposition. A small ventricular septal defect is seen between the lower border of the outlet septum (OS) and the trabecular septum (TS). (b) An equivalent echocardiographic plane in another patient with a similar defect. In this case the defect is much larger and there is posterior deviation of the outlet septum causing subpulmonary obstruction. AoV, aortic valve; PV, pulmonary valve; RV, right ventricle; LV, left ventricle.*

HEARTS WITH A COMMON ARTERIAL TRUNK

The ventricular septal defect in these hearts was morphologically similar to the doubly committed and juxta-arterial defect. In over half the hearts examined, the right ventricular margin of the defect included the central fibrous body (fig 12a). In other words, the defect was, in addition, perimembranous. The central fibrous body was identified as the area of continuity between the truncal and tricuspid valves. In the remaining hearts, the right ventricular margin of the defect was entirely muscular (fig 12b). In all the hearts examined, the left ventricular margin was partly made up by the area of fibrous continuity between the truncal valve and the mitral valve. In other words, there was no complete subtruncal infundibulum. Another feature of these defects was the degree of commitment of the truncal valve to the two ventricles. This was variable, but in the majority of cases the valve had more extensive right ventricular margins.

Discussion

Fully to describe a hole between the ventricles requires knowledge of several disparate features of its morphology. One of the reasons for disagreements about classification is that different groups have chosen different features as their basis.[11] All the features are important and all, therefore, should ideally be described. A description based upon cross sectional imaging techniques requires that the essential morphological features of each type of defect are identified or excluded. It does not matter in which imaging plane each morphological feature is sought. No feature should be considered to be specific to a single plane. The criteria we have identified can be applied in the interpretation of cross sectional echocardiography, but equally they are applicable to newer imaging methods such as magnetic resonance or computerised tomographic imaging, in which different imaging planes may be used. Our study has

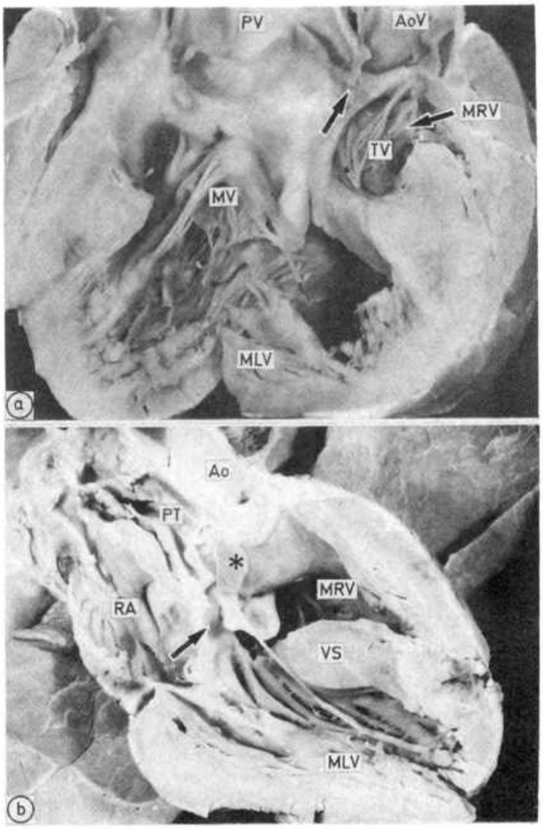

Fig 11 *These sections are both from hearts with congenitally corrected transposition (discordant atrioventricular and ventriculoarterial connections). The upper section (a), in a four chamber plane, shows a defect that is both perimembranous and doubly committed and juxta-arterial. The defect extends from continuity between the atrioventricular valves (MV and TV) and reaches to continuity between the arterial valves (PV and AoV (arrowed)). MLV, morphologically left ventricle; MRV, morphologically right ventricle. The lower section (b) is an oblique subcostal cut showing a perimembranous defect, roofed by pulmonary-mitral valve continuity (arrowed), with posterior deviation of the outlet septum (asterisk) giving subpulmonary obstruction. The left sided tricuspid valve has been replaced. Ao, aorta; PT, pulmonary trunk; RA, right atrium; VS, ventricular septum.*

convinced us that different types of defect cannot adequately be distinguished exclusively by the imaging plane in which they appear. This is unsatisfactory even in hearts with normal relations. In hearts with abnormal relations, such a rationale is useless. In contrast, describing defects according to morphological features specific to each type is independent of the relations of the cardiac chambers. Others have largely tried to interpret cross sectional echocardiographic images in the light of pre-existing classifications,[1 12 13] without taking into account the limitations inherent in cross sectional imaging. The great strength of these images is the fine anatomical detail that can be identified at the margins of defects.

DEFECTS BORDERING THE CENTRAL FIBROUS BODY

In hearts with concordant atrioventricular connection, with one exception (see below), the non-branching atrioventricular bundle is always related to the posteroinferior border of a perimembranous defect. With other types of ventricular septal defect the conduction axis follows its normal course.[14] Making the distinction between defects that are perimembranous and those that are not is, therefore, of great importance. In nearly every case this should be possible by cross sectional imaging. The criterion for diagnosing a defect as being perimembranous is the demonstration at one of its margins of fibrous continuity between the tricuspid valve and either an arterial valve or the mitral valve. To exclude perimembranous extension of a defect, the areas of fibrous continuity between the atrioventricular valves and the arterial and tricuspid valves must be shown not to form one of its borders. All perimembranous defects in hearts with normal connections are adjacent to the aortic valve, but not all "subaortic" defects are perimembranous. Demonstration that a defect is "subaortic" is not, therefore, sufficient to identify it as perimembranous. Continuity of the tricuspid and aortic valves at one margin of the defect must be established. In hearts with discordant ventriculoarterial connection, perimembranous defects are generally related to the pulmonary valve and so continuity between the pulmonary and tricuspid valves must be sought. No great artery is attached to the central fibrous body in hearts with a bilateral infundibulum. This feature can be demonstrated in cross sectional imaging by the absence of fibrous continuity between either arterial valve and either atrioventricular valve. Here, it is fibrous continuity between the two atrioventricular valves at one margin that is the sole marker for a perimembranous defect. Such a defect is not immediately adjacent to either arterial valve. Classifying such defects as "subaortic", "subpulmonary", or "non-committed" does not imply anything about the morphology of the defect but rather describes the extent to which the hole and the arterial valve are adjacent.[15]

When the remnant of muscle between the valves is very small a muscular defect could be mistaken for a perimembranous defect. The resolution of the imaging technique would be the critical factor. Failure of resolution would be unusual, however, and

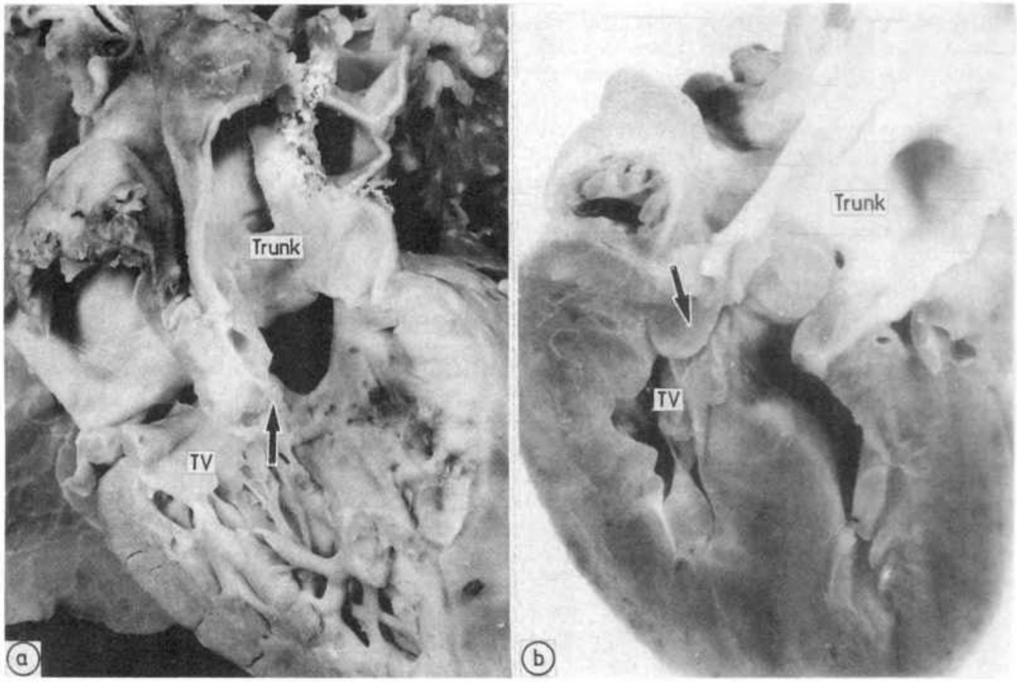

Fig 12 *These two sections of hearts with a common arterial trunk show (a) a perimembranous defect, with tricuspid (TV) truncal valve continuity (arrowed), and (b) a defect with a muscular posteroinferior rim (arrowed). This is the ventriculoinfundibular fold separating the truncal and tricuspid valves.*

in all the hearts we examined the muscle bordering the defect that separated the valves was substantial enough to be identified without ambiguity by current imaging techniques.

HOLES BORDERED BY CONTINUITY BETWEEN THE AORTIC AND PULMONARY VALVES

Doubly committed juxta-arterial defects are identified in cross sectional images by the presence at their superior margin of direct fibrous continuity between the leaflets of the aortic and pulmonary valves. A fibrous raphe between the two valves may be impossible to distinguish from a hypoplastic outlet septum. There is a group of defects, therefore, which will be difficult to place within the appropriate category. This distinction is, fortunately, not of great clinical importance. The two arterial valves are usually demonstrated to be at the same level, although this is not a critical feature of the doubly committed defect. Where there is a fibrous raphe or where the arterial sinus forms a margin of the defect[16] the valves may truly be offset.

The defect associated with a common arterial trunk is morphologically similar to the doubly committed defect. Identifying such a defect is part of the overall diagnosis of the cardiac anomaly. It may, in addition, be perimembranous, in which case there will be continuity between the truncal valve and tricuspid valve at the right ventricular margin of the defect.

MUSCULAR DEFECTS

A defect can only be said to have entirely muscular margins when it has been shown to be neither perimembranous nor doubly committed and juxta-arterial. Demonstrating that a defect has two muscular margins in a single cross sectional plane does not prove that muscle encompasses all its margins. If there is an overriding arterial valve, it is the right ventricular margin of the defect that is important in making the distinction between it being perimembranous or muscular. If there is a muscle bundle separating the tricuspid valve from the arterial valve, or valves, connected to the right ventricle, then it is this which protects the atrioventricular conduction axis.[14]

POSITION OF DEFECTS WITHIN THE SEPTUM

Cross sectional imaging can identify small perimembranous defects but cannot show whether they open into the inlet, outlet, or trabecular parts of the right ventricle. The morphological criterion for such distinction, the relation of the defect to the medial papillary muscle, cannot be used. In any case, this differentiation is of little value. None the less, attachments of the leaflets of the tricuspid valve around the defect indicate extension into the trabecular or inlets zones. This is not a feature of defects that extend to open solely between the subarterial outlets.[4] The term "perimembranous inlet defect" is best reserved for those large defects that extend to the crux of the heart and open between the inlets of both ventricles. These defects, roofed by the mitral and tricuspid valves in fibrous continuity, can readily be displayed by cross sectional imaging (fig 7).

Extension of perimembranous or muscular defects into the outlets can be demonstrated by the identification, at one margin, of an outlet septum, defined as a bar of muscle separating the space beneath the two arterial valves. As we have seen, demonstrating that the defect is adjacent to the aortic valve does not, in itself, indicate outlet extension. This is a feature of all perimembranous defects. In hearts with discordant ventriculoarterial connection, defects are commonly found at the lower border of the outlet septum. Distinguishing these from defects more apically placed in the trabecular septum requires an arbitrary judgement because there is no marker for the level of the junction of the outlet and trabecular septum.

Morphologically, perimembranous defects that extend into both the inlet and outlet parts of the right ventricle can be termed "confluent". Cross sectional imaging permits the identification of a very large defect that extends both to the crux and into the subarterial outlets. But a confluent defect that does not extend to the crux cannot be distinguished from a perimembranous outlet defect.

Muscular defects that do not open into the outlets may be identified as opening between the ventricular inlets if they are seen in the septum immediately beneath both atrioventricular valves and are separated from them by a bar of muscle. Other muscular defects can be described as trabecular. These defects can be further characterised by the distance they are from the apex in long axis sections. They can be multiple and have a tortuous course and hence, if small, may be difficult to detect in cross sectional images.[1 2 17]

OVERRIDING OF THE GREAT ARTERIES

There is a fundamental anomaly in septation in hearts with defects opening into both ventricular outlets. Overriding of a great artery is an important feature of some of these defects. The anomaly in these hearts should not be thought of as a simple hole in the ventricular septum. The leaflets of the overriding arterial valve form the roof of a conical space, the floor of which is the crest of the trabecular septum. This space has both right and left ventricular margins. The right ventricular margin corresponds to the defect in similar hearts without an overriding arterial valve. The left ventricular margin is commonly called the "defect" in hearts with double outlet of the right ventricle.[10] In these hearts, the ventricular septal defect should be considered as a three dimensional structure. All borders of the defect need to be described.[11] Only cross sectional imaging permits this.

Overriding of either great arterial valve is a relatively common feature of all defects opening between both ventricular outlets, be they perimembranous, muscular, or doubly committed and juxta-arterial. When present, it is a marker for outlet extension of a defect. The morphology of these defects is excellently demonstrated in coronal sections through the right ventricle,[18] but in such sections the extent of the override cannot be assessed. This is best done using long axis sections of the heart. Override of both great arteries can occur in the presence of a doubly committed defect.[19]

RELATION OF DEFECTS TO ARTERIAL VALVES

The terms "subaortic" and "subpulmonary" have been used to describe different aspects of the spatial relations between defects and the arterial valves. If this relation is described precisely, rather than classifying it in this way, ambiguity can be avoided. Hence, one type of "subaortic" defect can be described as a perimembranous defect immediately adjacent to the aortic valve,[2] while another "subaortic" defect could be described as opening between the subarterial outlets with overriding of the aortic valve.[15] In the context of double outlet from the right ventricle with bilateral infundibulum, the relation between the defect and the arterial valves cannot be predicted from the morphology of the defect. The classifications of "subaortic" and "subpulmonary" can be used to describe, in this context, a judgement by the observer about the feasibility of surgically connecting the defect to either arterial valve.[10] A full description of the relation of the defect to the arterial valves, however, is likely to be of more value than an arbitrary classification.

STRADDLING AND OVERRIDING OF THE ATRIOVENTRICULAR VALVES

Straddling and overriding of the mitral valve is also a feature of some outlet defects. Usually it is seen where there is a discordant ventriculoarterial connection or, as in this series, double outlet right ventricle with an overriding pulmonary valve, the so-called Taussig-Bing heart.[11 20] Straddling and overriding of the tricuspid valve is a feature of a particular perimembranous inlet defect. It is associated with considerable malalignment of the atrial septum relative to the muscular ventricular septum, which no longer extends to the crux. Identification of this defect is straightforward because of the septal malalignment. These defects are the only exception to the rule that, in hearts with concordant atrioventricular connection, the conduction axis is always posterioinferior to perimembranous defects.[20] Recognition of this anatomy is essential.

CONCLUSION

There is no need for a further classification of ventricular septal defects on morphological criteria and we have not attempted to produce one. Authors of the various existing classifications have chosen to emphasise different morphological features of the defects they studied, and they have, therefore, arrived at seemingly contradictory conclusions. We have not made a judgement that any one aspect of the morphology of ventricular septal defects is fundamental to their description. Ideally, all the morphological features need to be identified and described. We believe that, using the criteria we have described, it is possible virtually to achieve this aim. If, in this way, the morphology of a defect is completely described, its place in any of the diverse schemes of classification should be readily apparent. An additional problem is that some of the terms that have been used to describe the morphological features of ventricular septal defects are ambiguous, having been used by different workers to describe different features. To be of value descriptions need to be precise and so we have used terminology which describes the morphology of defects exactly and have discarded ambiguous terms. The great strength of cross sectional imaging is that it defines morphological detail at the margins of defects exceptionally well and, so, it is without equal in the clinical study of ventricular septal defects.

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Atrioventricular septal defect in prenatal life

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SUMMARY In a series of more than 3500 pregnancies referred for fetal echocardiography, 29 cases of atrioventricular septal defect were detected in the fetus. There was a chromosomal anomaly in 14 of these cases, left atrial isomerism in 12, and right atrial isomerism in two. Complete heart block was found in 11 of the cases with left atrial isomerism. Many associated cardiac abnormalities were found, particularly in the fetuses with atrial isomerism; the most common were double outlet right ventricle or aortic arch anomalies. The prognosis was poor in all patients with atrioventricular septal defect detected prenatally. Fifteen pregnancies went to term but there are only four survivors. Two of those have trisomy 21, a further patient has inoperable defects, and only one remains well and is awaiting corrective surgery for a partial atrioventricular septal defect.

The morphological characteristics of atrioventricular septal defect were first described by Peacock in 1846[1] and the association with trisomy 21 was noted by Abbott in 1924.[2] The accurate delineation of the atrioventricular defect by echocardiography is well recognised.[3] In recent years, fetal echocardiography has become established as a reliable predictor of congenital heart disease in prenatal life.[4 5] We have selected the cases of atrioventricular septal defect detected over the past seven years in order to present the associations in and outcome of these cases.

Patients and methods

From the start of 1980 to the end of 1986 we echocardiographically examined more than 3500 pregnancies in our department. We used either an Advanced Technical Laboratories Mark 3 sector scanner or a Hewlett-Packard 77020A phased array system with a 5 MHz transducer. The fetal heart was examined from multiple projections to identify all the cardiac connections. After Doppler examination of the heart became available in early 1985 this too was performed. Of 153 cases of structural cardiac abnormality identified in this sample, 29 were found to have deficiencies of the atrioventricular septum.

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Results

Of the 29 cases, 28 had a common valve orifice (the complete form) and one had separate valve orifices (the partial form or ostium primum defect). The gestational age ranged from 16 to 36 weeks. The reason for referral was non-immune fetal hydrops in 11 cases, previous family history of congenital heart disease in seven cases, fetal bradycardia in five cases, and the identification of extracardiac fetal abnormality in six cases. In the 26 cases where the sex of the fetus was known, 13 were male and 13 female. The diagnosis of atrioventricular septal defect was confirmed at postmortem examination in 21 cases. Postmortem was refused in four cases. Four patients are alive and the diagnosis has been confirmed by echocardiography in all and by cardiac catheterisation in three. In the first two years of the study, there was one false negative and one false positive prediction of partial atrioventricular septal defects.[4]

The atrioventricular septal defect was the only cardiac lesion in 8 cases. An example is shown in the figure. There was associated left atrial isomerism in 12 cases and right isomerism in two cases. There were seven patients with normal atrial arrangement and atrioventricular septal defect with other cardiac anomalies. Complete heart block was found prenatally in 11 of the 12 cases that had left atrial isomerism. Tubular hypoplasia of the aortic arch, aortic coarctation, or arch interruption was found in six cases. Double outlet right ventricle was found in seven cases—one of these also had right atrial isomerism and three had left isomerism. A discordant

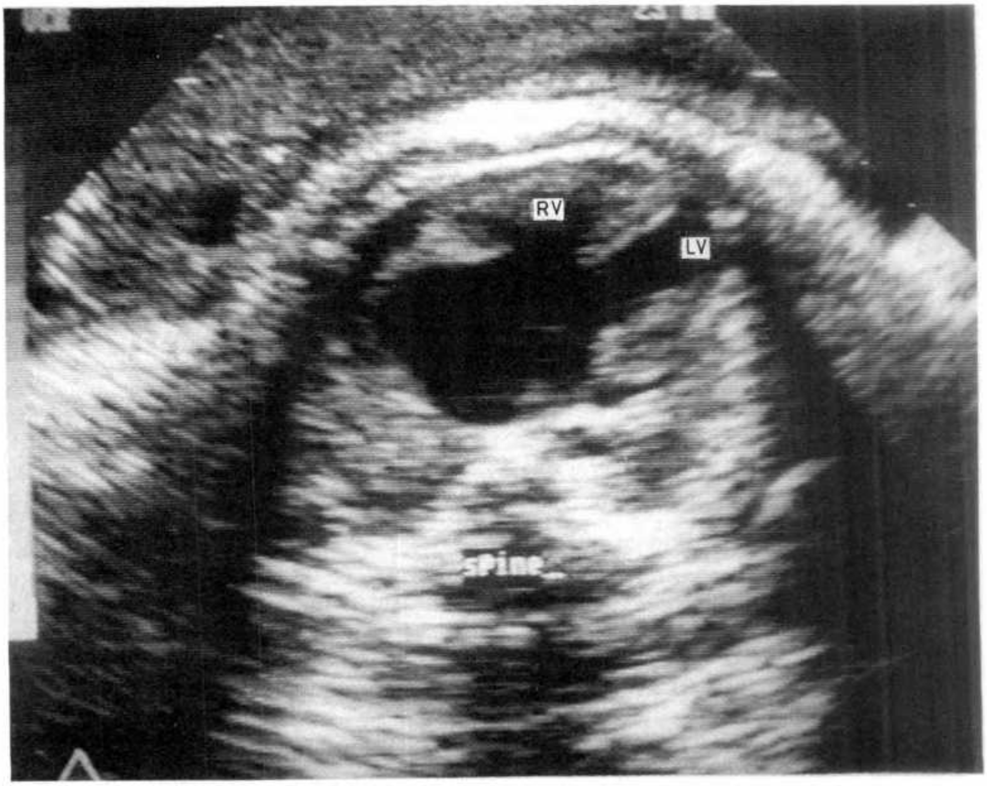

Figure *A heart in the four chamber projection showing opening of the common atrioventricular valve in diastole. The atrioventricular septal defect was the only cardiac lesion in this case.*

ventriculoarterial connection was present in two cases, aortic atresia in one case, and pulmonary atresia in three cases. Aortic (3) or pulmonary stenosis (3) was a feature of six cases. There was ventricular dominance to such a degree that the common valve was more than 50% committed to the right ventricle in two cases. Total anomalous pulmonary venous connection was found in both cases of right atrial isomerism.

The following chromosomal abnormalities were found in 14 cases: trisomy 21 in nine, trisomy 18 in three, extra fragment 22 in one, and Turner's syndrome in one. In this group there were two cases of diaphragmatic hernia, one case of duodenal atresia,

Table *The recurrent lesions in the patients with a family history of congenital heart disease*

Case No.	*Diagnosis in index case*	*Diagnosis in recurrent case*	*Associated anomalies in recurrent case*
1	TAPVC (+ fragment 22)	AVSD	Absent right lung, fragment 22
2	Critical PS	AVSD	Trisomy 21
3	TOF + anencephaly	AVSD	Trisomy 21
4	(a) VSD (b) PDS, PA	AVSD, DORV, PAtresia	Trisomy 18
5	Ebstein's, PS	AVSD, DORV, AAtresia, LAI	Hydrocephaly, polysplenia
6	(a) MAtresia, PAtresia, RAI (b) MAtresia, PAtresia, RAI	AVSD, PAtresia, TAPVC, RAI	Asplenia
7	DORV, VSD, PS	AVSD, DORC, RAI	None (patient alive)

In cases 4 and 6 there had been two previously affected children.
AVSD, atrioventricular septal defect; AAtresia, aortic atresia; DORV, double outlet right ventricle; LAI, left atrial isomerism; RAI, right aortic isomerism; PAtresia, pulmonary atresia; PS, pulmonary stenosis; PDA, patent ductus anteriosus; MAtresia, mitral valve atresia; TAPVC, total anomalous pulmonary venous connection; TOF, tetralogy of Fallot.

one case of exomphalos, one case with right pulmonary agenesis, and one case of cystic hygroma. There was one case of diaphragmatic hernia and atrioventricular septal defect with normal chromosomes. The atrioventricular septal defect was isolated in seven of the cases with trisomy 21. No case of chromosomal abnormality had atrial isomerism.

In seven cases the reason for referral for fetal echocardiography was a family history of congential heart disease. In none of these families was the previous lesion an atrioventricular septal defect. The table summarises data on these cases.

Fourteen pregnancies were terminated. Six of these fetuses had fetal hydrops and 11 had associated extracardiac or complex cardiac anomalies. There were four intrauterine deaths, all of whom were hydropic. There were four neonatal deaths (all within the first week of life) and three infant deaths. There are four survivors. Two of the survivors have trisomy 21 and one survivor presented in late pregnancy with fetal hydrops and has a partial atrioventricular septal defect with complete heart block and left atrial isomerism. The fourth survivor has right atrial isomerism with double outlet right ventricle, total anomalous pulmonary venous connection, and pulmonary stenosis.

Discussion

Nearly half of the cases of atrioventricular septal defect detected in this series had chromosomal anomalies, predominantly trisomy 21. The cardiac lesion tended to be isolated when a chromosomal abnormality was present but there were associated arch anomalies in some cases and frequently extracardiac anomalies. On the other hand, atrioventricular septal defects occurring with atrial isomerism tended to be associated with multiple and various cardiac anomalies and the extracardiac anomalies of asplenia of polysplenia that are expected with isomerism. As noted previously,[6] we never found Down's syndrome and isomerism in any of our cases. Only one case in the series had neither chromosome anomalies nor atrial isomerism; a diaphragmetic hernia caused early neonatal death in this fetus. Overall there was an association with conotruncal abnormalities in 10 (34%) cases of atrioventricular septal defect, which is consistent with other studies.[7 8] Complete heart block producing bradycardia was found in a total of 11 cases. But in only five of these 11 had fetal bradycardia been noticed by the referring obstetrician. There was a surprisingly strong association between complete heart block and left atrial isomerism (11 of 12 cases).

It is interesting that the pattern of recurrence of congenital heart disease was not concordant with the defect found in the previous child. In two young mothers the recurrence of congenital heart disease was associated with trisomy 21. One mother is a known carrier of a balanced translocation of trisomy 22 and she has now has three affected children, one with an atrioventricular septal defect and two with total anomalous pulmonary venous connection. In three of the remaining four patients in whom there was a recurrence of a defect, atrial isomerism was a feature, although isomerism was present in only one index case.

In the first two years of our study one false negative and one false positive diagnosis was made. Increased experience, modificetion of the echocardiographic method, and improved ultrasound equipment have prevented repetition of these errors. For example, complete diagnosis of structural heart disease is not attempted before 18 weeks' gestation and a defect must be confidently seen in at least two projections.

Pregnancies were terminated mainly because of multiple congenital abnormalities or when an atrioventricular septal defect was associated with severe fetal hydrops in early pregnancy. Those with this condition are known to have a poor prognosis and there were intrauterine deaths in four cases in which there was no intervention. Three of the four neonates who died had multiple congenital abnormalities and the fourth had complex heart disease. Two of the three infants who died had an operation. Only one of the four survivors has relatively minor heart disease that is amenable to surgery (partial atrioventricular septal defect with left atrial isomerism with no chromosome defect).

Thus patients with atrioventricular septal defect who come to the attention of the fetal echocardiographer are a biased sample who are more likely to have a chromosomal anomaly or complex heart disease and atrial isomerism. In both these circumstances the prognosis is very poor.

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Coarctation of the aorta in prenatal life: an echocardiographic, anatomical, and functional study

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SUMMARY In a prospective echocardiographic study of over 2000 pregnancies, 24 fetuses were found to have dilatation of the right ventricle and pulmonary artery when these structures were compared with those of the left heart. In 18 of these cases the diagnosis of coarctation or interruption of the aorta was correctly inferred from these findings. On direct echocardiographic examination of the aortic arch, arch hypoplasia or interruption of the aortic arch was recognisable prenatally in 10 of these 18 cases, most readily between 20–30 weeks' gestation. In 11 of 12 cases of aortic arch anomaly studied by Doppler echocardiography, a reduction in blood flow in the ascending aorta was demonstrated. The intracardiac appearances were suggestive of coarctation but the Doppler findings were within normal limits in two further cases which later proved to be normal. A diaphragmatic hernia was found in four fetuses and the intracardiac echocardiography and Doppler findings were the same as those found in fetuses with aortic coarctation. Five cases of coarctation were overlooked on the prenatal echocardiogram but these were found at follow up of the infants.

Thus coarctation of the aorta can be diagnosed prenatally, although the condition may be missed or incorrectly predicted by the criteria examined in the present study. Reduced aortic blood flow is a demonstrable feature of aortic arch abnormalities but it is found in other conditions that are not associated with coarctation.

During our total experience of fetal echocardiography we have had the opportunity to describe both normal and abnormal cardiac anatomy[1,2] and to follow the development of cardiac structure in the normal fetus.[3] More recently we have been able to define the normal flow patterns during fetal life.[4] Earlier in this programme we reported on the echocardiographic diagnosis and evolution of a case of coarctation of the aorta recognised initially at 20 weeks' gestation.[5] This case showed that coarctation of the aorta could be diagnosed prenatally but raised questions about the prevailing theories of its development. This case prompted a prospective study of the diagnosis of fetal coarctation in 2000 pregnancies that we subsequently examined and in which we studied development of the heart and great arteries in those suspected cases which went to term.

Patients and methods

We used either an Advanced Technical Laboratories Mark III or a Hewlett-Packard 77020A sector scanner to study 2029 fetuses. The fetal echocardiography programme including Doppler investigation was approved by the ethics committee and each mother gave informed consent to the study. The whole echocardiogram was stored on videotape. The examination was repeated if all the necessary information could not be obtained at one sitting or if an abnormality was found and the pregnancy continued.

Neonates were examined by a paediatric cardiologist or paediatrician. All fetuses that died in utero and the products of termination were examined at necropsy.

The echocardiographic signs that we particularly noted were: (*a*) relative sizes of the right and left ventricles as measured at the level of the atrioventricular valve orifices in a frozen frame diastolic image of a four chamber view of the fetal heart (the range (mean (1 SD)) for this ratio, based on 80 normal fetuses is 1·1 (0·09)[4]); (*b*) relative sizes of the

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pulmonary artery and aorta. These measurements were made at the origin of each vessel with the image frozen in systole. The range (mean (1 SD)) for this ratio based on 80 normal fetuses is 1·2 (0·18); (*c*) the appearance of the aortic arch and isthmus. This was a subjective evaluation of the arch structures in relation to the sizes of adjacent vessels such as the arterial duct and branch pulmonary arteries.

When any intracardiac or aortic arch abnormality was suspected we also examined the atrioventricular and arterial valves by Doppler echocardiography when this facility became available. Blood flow was then estimated as previously described.[4]

Results

Twenty four of the 2029 fetuses had relative right ventricular and pulmonary artery dilatation as judged by cross sectional echocardiography. The diagnosis of coarctation was suspected from these signs in 16 cases. In no case could a discrete coarctation "shelf" itself be positively identified on direct echocardiographic examination of the arch, but convincing arch hypoplasia could be identified in eight patients. A discrete shelf lesion was, however, found at postnatal operation in two, at necropsy in 10, and at both in four. In two further cases, the intracardiac findings were the same as those with coarctation but the arch was seen to be interrupted. A prospective echocardiographic diagnosis of aortic arch abnormality was correctly made, therefore, in 18 of the 24 cases.

In 17 of the 24 patients studied by Doppler three had two studies and one had three studies. Tricuspid flow was more than twice mitral flow in all 22 examinations. Blood flow in the ascending aorta was measured in 20 studies. This measurement was below the normal range for the gestation in 12 and

Table *Prospective diagnoses*

Case No	*Diagnosis*	*Gestation (wk)*	*RV LV**	*PA Ao†*	*Aortic flow (ml/min)*
			Prospective diagnosis		
1	C	23	1 74	2 46	—
		29	1 46	1 72	—
		37	2·2	1·89	264
2	C	21	1·6	1 44	38
3	C	23	1 4	1 55	76
4	C (xo)	18	1 4	1 8	10
5	C	18	1 15	1 66	17
		24	1 49	1 79	33
6	C (xo)	24	1 33	2 07	30
7	C (trisomy 18)	32	1 2	1 72	181
8	C	23	1 39	1 5	74
		28	1 24	1 5	140
9	C (xo)	19	1 68	1 5	21
10	C (trisomy 18)	30	1 6	1 9	66
11	C + VSD	38	1 79	1 5	900
12	C	36	1 47	1 38	—
13	I + VSD	19	1 73	3 9	20
14	I+ VSD	24, 34	1 2	2 3	—
15	C	18	+	+	—
16	C + VSD	24, 32	+	+	—
17	C + VSD	18, 24, 32	+	+	—
18	C (xo)	18	+	+	—
19	DH	38	+	+	—
20	DH	26	1 43	1 57	63
		33	2 1	1 74	139
21	DH	27	1 33	1 9	70
22	DH	35	1 2	1 5	218
23	Normal	32	1 19	1 6	244
24	Normal	32	1 36	1·39	262
			False negative diagnoses		
1	C	20	no	no	—
2	C	18	1 04	1·25	—
		24	1 15	1 17	—
3	C	18	1 55	1 8	—
		24	1·56	2 3	—
4	C	24	1 2	1·6	—
5	C	18, 24	+	+	—

+ The videotape was recorded on equipment from which retrospective measurements cannot be made but on gross examination an increase of the RV LV and PA Ao ratios was apparent.
*Normal range 1 1(0 09).
†Normal range 1 2(0 18).
C, coarctation; I, interruption, VSD, ventricular septal defect; xo, Turner's syndrome.

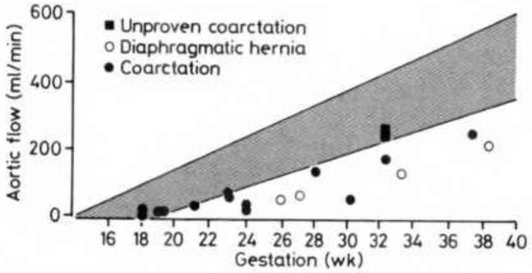

Fig 1 *Relation between aortic blood flow and gestational age. The shaded area shows the normal range. The values for each of the abnormal groups are shown. In both real aortic arch lesions and in diaphragmatic hernias the aortic flow is significantly below the normal mean* ($p > 0{\cdot}001$).

below the mean in a further five examinations. Doppler examination showed reduced blood flow in the aorta in 11 of 12 fetuses with confirmed coarctation or interruption of the aorta. Figure 1 shows aortic flow in each of these studies. In one fetus with coarctation, the aortic flow was much greater than normal mean value (case 11 in table).

In four of the 24 cases the fetal scan showed a diaphragmatic hernia (fig 2). Three of these had both anatomical and flow features consistent with coarctation. In one only the anatomical features were known because Doppler was not available at the time of examination. Underdevelopment of the left heart is known to occur with diaphragmatic hernia.[6 7] These intracardiac findings were therefore considered to be secondary to the diaphragmatic lesion.

Two fetuses had cross sectional echocardiographic appearances suggesting coarctation but without any abnormality of the aortic arch on direct examination. It was felt that in these two cases a diagnosis of coarctation could not be excluded. The Doppler flow patterns were within normal limits in both cases. These two fetuses were normal at postnatal follow up.

The table shows ages at which the echocardiographic abnormalities were detected. The intracardiac signs were detected at presentation irrespective of gestational age. The aortic arch was difficult to assess conclusively in the youngest and the oldest fetuses. Of the total group of 18 cases of arch abnormality, eight aortic arches were identified as hypoplastic and two were seen to be interrupted. In a further three cases, the arch was not seen adequately for assessment. In the remaining five cases the appearance of the arch was within normal limits. In the seven cases of coarctation studied serially to term the size of the arch and isthmus relative to other cardiac structures decreased towards term in three. The earliest that coarctation or interruption was suspected on cross sectional echocardiography was 18 weeks, and seven of the abnormal fetuses were detected by 20 weeks. The abnormal aortic flow pattern, however, was more convincingly outside the normal range in studies after 20 weeks' gestation (fig 1).

Coarctation was not diagnosed prospectively in five of the 2029 patients. These cases presented with this condition after birth. Review of the fetal echocardiogram showed normal cross sectional echocardiographic features in two. The features of coarctation had been overlooked in the other three. Doppler interrogation of all the cardiac valves had not been performed in these five cases because in our centre this is not a routine investigation unless coarctation is suspected antenatally.

Discussion

Our results show that it is possible to recognise coarctation of the aorta as early as 18 weeks' gestation. Recognition depends on integrating many features. These include analysis of the relative sizes of the two ventricles and great arteries and the evaluation of the aortic arch in fetal life. The right ventricle is normally slightly larger than the left and the pulmonary artery slightly larger than the aorta.[4] If these features are more pronounced than normal coarctation should be suspected. In the past the evaluation of the arch and isthmus relative to the arterial duct and pulmonary arteries was subjective. Recent measurements of these structures in the normal fetus will allow us to be more objective in

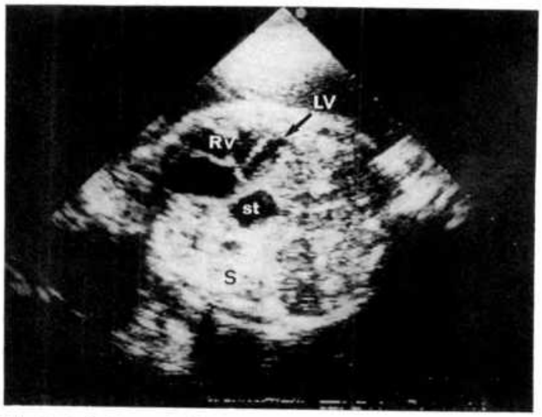

Fig 2 *The heart in the four chamber projection showing the relative hypoplasia of the left ventricle (LV) that is caused by the stomach and bowel occupying the whole of the left thorax. The heart lies in the right chest. s, spine; st, stomach; RV, right ventricle.*

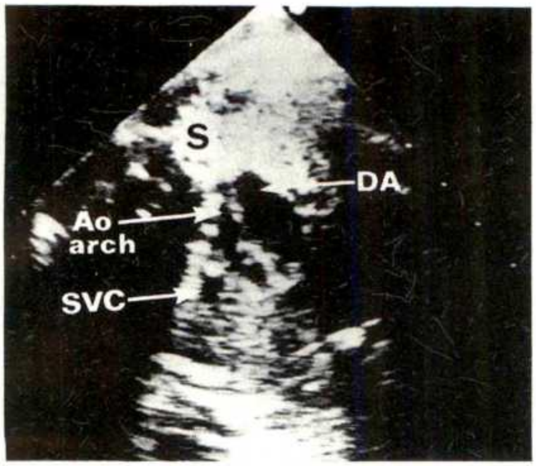

Fig 3 *The diameter of the crest of the aortic (Ao) arch in this patient is much smaller than that of ductus arteriosus (DA). There was severe arch hypoplasia in association with coarctation in this case. SVC, superior vena cava.*

future (unpublished observations). Measurement of arch structures may also help to identify those cases with less severe arch hypoplasia because some hypoplasia is normal. If diminished aortic flow is recorded on Doppler the likelihood of coarctation is increased. The combined findings give a high degree of accuracy.

On occasion, the relative sizes of the ventricles and great arteries in late pregnancy may suggest coarctation and it may be difficult to visualise the aortic arch. Previously, we sought the longitudinal view of the fetal arch for examination. This is similar to the view seen postnatally. This was difficult to obtain in every patient, especially in late pregnancy or in some cases where the fetus was lying in an infavourable position. Latterly, we have analysed horizontal views of the thorax, which allow us to see the arch and arterial duct in the same section.[8] This permits direct comparison of the size of these structures. The crest of the aortic arch and the arterial duct should be of similar size. Figure 3 shows one of the cases of coarctation where the arch was severely hypoplastic. This view of the arch is more readily obtainable in all fetuses, irrespective of fetal age or position. Use of this approach may improve our record of adequate examination of this site.

There was >2:1 flow across the tricuspid and mitral valves in all cases of coarctation or interruption of the aorta. The upper limit of the ratio in the normal fetus is 1·8:1.[4] In the two cases of suspected coarctation absolute aortic flow measurement established that these were in fact normal cases.

In the five false negative diagnoses of coarctation, retrospective examination of the videotaped echocardiogram showed normal anatomical features in two cases (cases 1 and 2 in table). One of these cases presented without symptoms after the neonatal period, while the other had a discrete coarctation with no isthmal narrowing. This raises the possibility of two forms of coarctation, one being haemodynamically important in fetal life and usually associated with isthmal hypoplasia, and the other arising in postnatal life, perhaps produced by or dependent on ductal closure for its complete development. All the cases of coarctation predicted prenatally had a degree of isthmal hypoplasia postnatally or at necropsy whether this feature had been clearly recognised echocardiographically or not. Those cases with severe arch hypoplasia were most readily recognisable on the prenatal echocardiogram.

Echocardiographic and Doppler findings in four cases of diaphragmatic hernia were similar to the findings in coarctation. We attributed the low flow through the left heart with the consequent right ventricular and pulmonary artery dilatation to left heart compression by the diaphragmatic hernia. An alternative explanation is that the diminished pulmonary venous return caused by lung hypoplasia may reduce flow through the left ventricle and thus lead to underdevelopment of this chamber. The fact that in these cases a major disturbance of left ventricular flow with appreciable decrease in the size of the arch was not associated with coarctation casts doubt upon the flow dependent causation of coarctation. One of the cases of coarctation had aortic flow well above the normal range. This fetus had a large ventricular septal defect and severe right ventricular dysfunction, which may account for this finding.

We conclude that coarctation of the aorta can be diagnosed by prenatal echocardiography. This finding challenges the proposed role of the closure of the arterial duct in the development of aortic coarctation. False positive diagnosis, and perhaps also false negative diagnosis, can be avoided if Doppler evaluation of aortic blood flow is included in the fetal examination. It may not be possible, however, to recognise prenatally some milder forms of coarctation. The degree of decrease in aortic blood flow may contribute to the severity of arch hypoplasia occurring in association with coarctation. The reduced aortic flow none the less, must be secondary to the presence of the anatomical shelf lesion because other conditions occurring in utero that produce diminished aortic blood flow, such as diaphragmatic hernia, do not lead to development of coarctation.

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Internal mammary artery conduit: an additional surgical procedure in difficult coarctation of the aorta

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SUMMARY Between October 1986 and February 1987 two young men with coarctation of the aorta and a hypoplastic isthmus were treated by a combined resection and isthmusplasty with implantation of the left internal mammary artery to the distal aorta. An appreciable drop in the systolic gradient was seen in both patients after the mammary artery anastomosis and haemodynamic variables across the repair continued to improve postoperatively. Digital transvenous subtraction angiography five months after operation showed a satisfactory mammary artery conduit across the repaired coarctation.

The choice of operation for aortic coarctation is influenced by the patient's age, anatomical abnormality, and the surgeon's experience.[1 2] Several different techniques have been described: resection and end to end anastomosis, subclavian flap aorto plasty, patch aortoplasty with prosthetic or biological grafts, Vosschulte's aortoplasty, and prosthetic tubular conduit between the ascending and descending parts of the aorta.[3-5] Severe hypoplasia of the isthmus in the adult patient may limit the extent of resection because in an attempt to maintain the collaterals to the spinal cord every effort is made to limit the number of intercostal vessels ligated or divided. A wider anastomosis may be achieved by isthmusplasty, but in severe cases of hypoplasia this alone may not reduce the systolic gradient to an acceptable value.

In these circumstances implantation of the left internal mammary artery to the distal aorta is a simple but effective additional procedure to achieve better flows beyond the repair.

Case reports

PATIENT 1

A 27 year old symptom free man was found to have a coarctation of the aorta at a routine medical examination. Blood pressure recordings showed a systolic gradient of 90 mm Hg (170/110 in the arm and 80/40 in the leg). A tight coarctation with hypoplastic aorta was confirmed at aortography. At operation, through a left thoracotomy, the coarctation was excised and repair effected by isthmusplasty. The systolic gradient fell from 90 mm Hg to 30 mm Hg. The left internal mammary artery was therefore dissected off the chest wall and the distal end was anastomosed to the distal aorta with 5 O Prolene sutures over a side clamp on the aorta. The internal diameter of the internal mammary artery was 10 mm and the final gradient across the repair was 9 mm Hg.

Paradoxical hypertension developed immediately after operation; this responded to β blockade. His recovery was otherwise uneventful and the arm to leg systolic gradient had disappeared on subsequent examination eight days after operation. His condition was entirely satisfactory at an outpatient review four months later. Patency of the internal mammary artery was confirmed by digital transvenous subtraction angiography five months after the repair (figure).

PATIENT 2

A 28 year old symptom free man was found to have coarctation of the aorta at a routine medical check up. His aortogram showed a coarctation of a long segment and hypoplasia of the isthmus, with a systolic pressure gradient of 65 mm Hg across the coarctation. At operation, through a left thoracotomy, the repair was effected by resection of the coarctation and isthmusplasty, and the systolic pressure gradient fell to 41 mm Hg. The left internal mammary artery, which had an internal diameter of 6 mm, was

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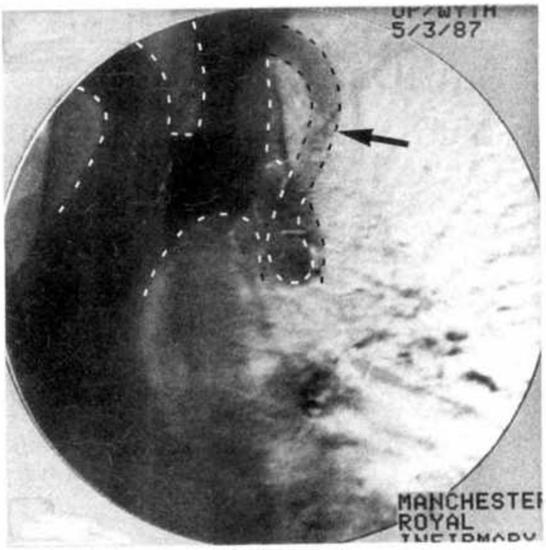

Figure *Transvenous digital subtraction angiogram showing the internal mammary artery conduit across the site of the repaired coarctation.*

dissected off the chest wall and implanted on to the distal aorta with 5 O Prolene sutures by means of a side clamp on the aorta. Subsequent recordings showed a systolic gradient of 20 mm Hg. This patient developed paradoxical hypertension, which responded to β blockers. The arm to leg systolic gradient was < 10 mm Hg before his discharge nine days after operation.

Discussion

The object of any corrective operation for aortic coarctation is a zero gradient across the repair. There are no absolute guidelines, but most surgeons regard a systolic gradient of < 20 mm Hg in an adult or 10 mm Hg in a child as acceptable.[6-8] In a series of cases of recurrent coarctation, Sweeny *et al* considered an arm to leg systolic gradient of $\geqslant 30$ mm Hg as an indication for reoperation.[9]

Ischaemic injury to the spinal cord is a known complication of operation for coarctation, and this is more common in reoperations.[2,10] Even though no definite correlation has been established between the extent of spinal cord ischaemia and the number of intercostal arteries divided, most surgeons believe that every effort should be made to achieve an adequate anastomosis with division of as few intercostal vessels as possible. Other factors that influence damage of the spinal cord include the anatomical abnormalities of the anterior spinal artery and the duration of aortic cross clamping.

A relatively small aorta and the proximity of large collaterals are common characteristics of the hypoplastic isthmus. Resection of the abnormal tissue of coarctation may be justified in an attempt to prevent recurrence. Isthmusplasty will increase the effective diameter of the anastomosis. In severe hypoplasia, however, the final gradient may still remain high because the size of the anastomosis is limited. The systolic gradients after isthmusplasty in our two patients were 30 and 40 mm Hg respectively. The large left internal mammary artery was therefore dissected off the chest wall and implanted to the distal aorta in both patients; this reduced the systolic gradient to 9 mm Hg and 20 mm Hg respectively, indicating better flows beyond the site of repair.

Use of the internal mammary artery as a free patch graft has been described.[11,12] The technique we have described has the advantages of a relatively easy anastomosis over a side clamp and of a very large and convenient collateral being used as a conduit. We must emphasise, however, that this technique is unsuitable for young patients with coarctation because their internal mammary arteries are small. The fragility of the intercostal vessels in aortic coarctation is well known. We noticed that even though these vessels had aneurysmal dilatation at their origin from the aorta, they were of remarkably good quality where they communicated with the internal mammary artery. These communications were divided between Ligaclips and then each end was reinforced with 6 O Prolene sutures for added safety. We found that vessel wall hypertrophy of the dilated mammary artery made it safe to anastomose to the aorta. We were quite satisfied with the condition of the mammary artery as visualised on the digital transvenous subtraction angiogram (figure). Caution should, however, be exercised if this patient has a left lung resection in later years because of the position of the mammary artery in relation to the left hilum.

We recommend the implantation of the left internal mammary artery to the distal aorta in adults with coarctation and a hypoplastic isthmus if the systolic gradient remains $\geqslant 30$ mm Hg after the repair. It is simple but effective and does not increase morbidity because the anastomosis can be constructed without cross clamping of the aorta.

We thank Dr Richard Fawcett for his kind assistance with the investigations.

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Coronary heart disease in the Medical Research Council trial of treatment of mild hypertension

MEDICAL RESEARCH COUNCIL WORKING PARTY ON MILD HYPERTENSION

SUMMARY Seventeen thousand three hundred and fifty four mildly hypertensive people with diastolic blood pressures between 90 and 109 mm Hg at screening were randomised to active treatment, with bendrofluazide or propranolol, or to placebo tablets. They were followed for a maximum of five and a half years, giving a total of 85 572 patient-years of observation. There were 456 myocardial infarctions or sudden coronary deaths. Drug treatment did not affect the overall rate of coronary events. Rates per thousand person-years were 8·3 and 9·0 in men and 1·8 and 1·7 in women in the active treatment and placebo groups respectively. Event rates were much higher in smokers than in non-smokers on placebo treatment (12·6 and 7·5 in men and 3·5 and 1·0 in women in smokers and non-smokers respectively). An analysis of subgroup results showed a lower event rate in non-smoking men on propranolol than in non-smokers on placebo (5·0 and 7·5 per thousand person-years respectively). Bendrofluazide had no apparent effect on the event rate. The interaction between the type of treatment (propranolol, bendrofluazide, or placebo) and smoking in determining the coronary event rate was not statistically significant, however. The incidence of electrocardiographic changes of silent infarction—that is major Q/QS abnormalities—differed little with sex, smoking habit, or treatment with either active drug.

One of the main aims of the Medical Research Council's trial of the efficacy of antihypertensive treatment of patients with mild hypertension was to determine whether such treatment, with either a thiazide diuretic or a β blocker, would be associated with a change in the incidence of coronary events.[1]

While the Medical Research Council study was in progress the results of both the Hypertension Detection and Follow-up Program[2] (HDFP) and the Australian National Blood Pressure Study[3] (ANBPS) appeared. Both these trials showed some reduction in fatal myocardial infarctions in treated groups, although extrapolation from the results of the Hypertension Detection and Follow-up Program was difficult because the study did not include an untreated control group and generalisation from the Australian National Blood Pressure Study was of limited value because rather few coronary events occurred in that trial. Another report, from the Multiple Risk Factor Intervention Trial (MRFIT) suggested that thiazide treatment of people with abnormal electrocardiograms might increase deaths from coronary heart disease.[4] Overall, the picture remained unclear and it was postulated that adverse metabolic effects of commonly used antihypertensive drugs might counteract any beneficial effects of pressure lowering on coronary heart disease.[5]

The Medical Research Council trial data suggested a further complexity, in that retrospective subgroup analysis indicated that propranolol might perhaps protect against coronary events, though in non-smokers only.[1] This tentative suggestion received some support from the independent finding in the International Prospective Primary Prevention Study in Hypertension (IPPPSH) that the rate of cardiac events was lower in non-smoking men randomised to antihypertensive treatment, including oxprenolol, than in those whose antihypertensive regimen did not include a β blocker.[6]

Patients and methods

These have been described elsewhere[1] and only the

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essential details are given here.

The 17 354 participants were men or women aged 35–64 years at entry, with sustained diastolic (V) pressures 90–109 mm Hg over the screening period. People with a history of definite myocardial infarction within the previous three months, angina, signs of cardiac failure, or electrocardiographic evidence of a silent myocardial infarction or of left bundle branch block were ineligible. Patients were randomly allocated at entry to groups taking either bendrofluazide (n = 4297) or propranolol (n = 4403) or placebo tablets (n = 8654). All subjects had a resting 12 lead electrocardiogram recorded at entry and every year subsequently and had serum potassium measured at entry and at one, three, and five years afterwards; those randomised to take bendrofluazide had additional potassium measurements three months, two years, and four years after entry. If serum potassium was below 3 5 mmol/l at entry examination, the patient was excluded from the trial. If the concentration fell on treatment to less than 2·4 mmol/l, as happened in a few patients, diuretic treatment was stopped and oral potassium chloride was prescribed.

Each electrocardiogram was coded according to the Minnesota criteria[7] so that important abnormalities could be recorded on computer. Each tracing was read by two observers who were blind to the treatment regimen; the second reader was also blind to the first reader's coding. If these two readers disagreed, a third reader was used. Only the first recorded change in any individual's electrocardiogram coding was used to calculate the incidence or reversion rates of electrocardiogram abnormalities. For instance, a person whose entry electrocardiogram was free of abnormal Q waves but who showed such waves at the first anniversary was counted as an incidence case whether or not the change persisted in subsequent recordings. Similarly, a person whose tracings at entry and first anniversary showed abnormally tall R waves, but whose second anniversary tracing did not, was counted as a reversion case whatever the picture in the later years.

Myocardial infarction was defined according to World Health Organisation criteria.[8] Sudden death was defined as death within one hour of the onset of symptoms and was assumed to be caused by coronary heart disease unless postmortem examination showed some other cause. In the case of people found dead, it was usually possible to ascribe death to a sudden or not sudden category. In the small number of cases in which the timing was unknown, the case was included in the not sudden group. All events were assessed by an independent arbiter who was blind to the treatment regimen.

STATISTICAL ANALYSIS

(a) *Calculation of risk factors*

Multiple logistic regression was done on the conventional risk factors—age, systolic and diastolic blood pressure, serum cholesterol concentration, body mass index (body weight/height^2 in kg/m^2), electrocardiographic signs of ischaemia, and the number of cigarettes smoked. These factors were measured at entry to the trial and at intervals throughout the trial. For age and for electrocardiographic signs of ischaemia, entry data were used, while for the other variables the mean observed values throughout the trial were used.

The use of such in-treatment mean values increases the sensitivity of the analysis, and also gives estimates of relative risk that are unbiased by the effect of the selection process at screening. Calculated relative risks with respect to entry variables are to some extent biased by selection: for instance, despite repeated measurements being taken before entry, pressure still fell markedly during the early weeks of participation,[1] presumably as the pressor effect of taking part in the trial diminished and as a result of regression to the mean. The data for the range of diastolic pressure once this process of familiarisation was largely complete indicate that the underlying range of pressure in trial subjects was less than that used as the entry criterion. The relative risk calculated for a given change of diastolic pressure in the present data is therefore correspondingly underestimated.

(b) *Significance of results*

Care is needed when p values given as "significant" or not are interpreted. If the comparison is of prime importance, and might well have been considered so before the data were analysed, then it is appropriate to take the p values at face value and adopt the conventional 0·05 value as the critical point, and this is the level indicated by the term "significant" used in the text. Interpretation, even of "significant" results of clear a priori importance, should be modified if the comparison is one of a number of correlated comparisons. In the absence of a priori importance a result with even a low p value should be treated with caution as it has been obtained in the course of many subgroup analyses on many different variates. An appreciably lower p value would be needed in such a case before significance could be ascribed to the relevant differences. These considerations explain why some comparisons have been fully discussed in the text while others have not. For full information an indication of the p value has been given in the tables for levels of 0 05 to 0·1 in addition to the conventional mention of values $<0{\cdot}05$.

Table 1 *Coronary events by sex and regimen (numbers and rates/1000 patient-years)*

	Both sexes *Active treatment*		*Placebo*	
Both treatments together.				
No	8 700		8 654	
Patient-years	42 911		42 661	
	No	*Rate*	*No*	*Rate*
All coronary events	222	5·2	234	5·5
Non-fatal	116	2·7	137	3·2
Fatal	106	2·5	97	2·3
Sudden	49	1·1	45	1·1
Not sudden	57	1·3	52	1·2

	Men *Active treatment*		*Placebo*		*Women* *Active treatment*		*Placebo*	
Both treatments by sex.								
No	4 523		4 525		4 177		4 129	
Patient-years	22 129		22 190		20 782		20 471	
	No	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*
All coronary events	184	8·3	200	9·0	38	1·8	34	1·7
Non-fatal	96	4·3	113	5·1	20	1·0	24	1·2
Fatal	88	4·0	87	3·9	18	0·9	10	0·5
Sudden	41	1·8	41	1·8	8	0·4	4	0·2
Not sudden	47	2·1	46	2·1	10	0·5	6	0·3

	Men *Bendrofluazide*			*Propranolol*			*Placebo*			*Women* *Bendrofluazide*			*Propranolol*			*Placebo*		
By individual drug and sex:																		
No	2 238			2 285			4 525			2 059			2 118			4 129		
Patient-years	10 945			11 184			22 190			10 274			10 508			20 471		
	No	*Rate*	*SE*	*No*	*Rate*	*SE*	*No*	*Rate*	*SE*	*No*	*Rate*	*SE*	*No*	*Rate*	*SE*	*No*	*Rate*	*SE*
All coronary events	99	9·0	0·9	85	7·6	0·8	200	9·0	0·6	20	1·9	0·4	18	1·7	0·4	34	1·7	0·3
Non-fatal	49	4·5	0·6	47	4·2	0·6	113	5·1	0·5	11	1·1	0·3	9	0·9	0·3	24	1·2	0·2
Fatal	50	4·6	0·6	38	3·4	0·6	87	3·9	0·4	9	0·9	0·3	9	0·9	0·3	10	0·5	0·2
Sudden	29	2·6	0·5	12	1·1	0·3	41	1·8	0·3	4	0·4	0·2	4	0·4	0·2	4	0·2	0·1
Not sudden	21	1·9	0·4	26	2·3	0·5	46	2·1	0·3	5	0·5	0·2	5	0·5	0·2	6	0·3	0·1

Results

MYOCARDIAL INFARCTION AND SUDDEN DEATH

Table 1 shows the numbers and attack rates of fatal and non-fatal coronary events, with fatal events divided into sudden and not sudden, for both sexes and both treatments together and separately. There was a total of 456 events, 222 in people on active treatment (5·2 per thousand person-years) and 234 in those in the placebo group (5·5 per thousand person-years), giving no indication that the antihypertensive regimen had affected coronary event rates overall.

In all there were 384 events in men and only 72 in women (cumulative five and a half year percentages 4·7 and 0·9, rates 8·7 and 1·7 per thousand person-years respectively). All categories of coronary events—that is, non-fatal and fatal and both sudden and not sudden death—were more common in men than in women. One hundred and seventy five (46%) events in men were fatal, and of these 82 (47%) were sudden deaths. In women, 28 (39%) of all events were fatal, and 12 (43%) fatal cases were classified as sudden death. There were no significant differences between attack rates, in either sex, in any category, or on either active drug compared with placebo. Analysis by "on treatment" (as opposed to "as randomised") categories gave closely similar results.

Bendrofluazide in men—The overall coronary event rate of 9·0 per thousand person-years was the same as that in the placebo group (SE on bendrofluazide 0·9 and on placebo 0·6). When the events were subdivided into fatal and non-fatal, and sudden and not sudden, there were some small differences between the bendrofluazide and placebo rates, none of which approached statistical significance: (*a*) a small mean (SE) reduction in non-fatal event rates on the thiazide compared with the placebo (4·5 (0·6) *vs* 5·1 (0·5) per 1000 person-years); (*b*) a small increase in fatal event rates on the thiazide (4·6 (0·6) *vs* 3·9 (0·4) per 1000 person-years); (*c*) a small increase in sudden death rates on the thiazide (2·5 (0·5) *vs* 1·8 (0·3) per 1000 person-years); (*d*) a small increase in the percentage of all events on the thiazide that were sudden deaths (29% *vs* 21%). Analysis by "on treatment" categories gave closely similar results.

Propranolol in men—The mean (SE) overall rate was slightly but not significantly lower in this group than in the placebo group (7·6 (0·8) and 9·0 (0·6) per thousand person-years respectively). Other comparisons with the rate in the placebo group showed: (*a*) a small decrease in non-fatal event rates on propranolol (4·2 (0·6) *vs* 5·1 (0·5) per 1000 person-years); (*b*) a small decrease in fatal event rates on propranolol (3·4 (0·6) *vs* 3·9 (0·4) per 1000 person-years); (*c*) a small decrease in sudden death rates on propranolol (1·1 (0·3) *vs* 1·8 (0·3) per 1000 person-years); (*d*) a small decrease in the percentage of all events on propranolol that were sudden deaths (14% *vs* 21%).

None of these differences approached conventional levels of significance. Whatever the treatment regimen, all rates in women were small and further analyses were uninformative.

Risk factors—Some information has already been published.[1] More sensitive analyses have since been possible based on exact values (without categorisation) of on-treatment variables where appropriate, and some changes in the apparent importance of certain factors have become evident.

Table 2 shows the relative risks in relation to the conventional risk factors in men. Certain variables,

Table 2 *Relation between conventional risk factors and the development of coronary events*

	Age 5 yr increase†	*Cholesterol (1 mmol/l increase)**	*Smoking (20/day increase)**	*Ischaemic entry ECG*‡	*SBP (10 mm Hg increase)*	*DBP (4 mm Hg increase)*	*Quetelet's Index (1 kg/m² increase)**	*Treatment effect*
Men, active treatment all events								
RR	1·39	1·38	2·65	2·25	NS	NS	NS	Bendrofluazide versus propranolol, NS
95% CI	1·21–1·60	1·16–1·64	1·90–3·70	1·22–4·15				
p value	<0·0001	0·0003	<0·0001	0·0083				
Men, placebo group, all events								
RR	1·31	1·28	1·89	2·44	1·21*¶	1·14*¶	NS	—
95% CI	1·14–1·52	1·07–1·52	1·31–2·61	1·45–4·24	1·03–1·42	1·00–1·32		
p value	0·0002	0·0061	0·0001	0·001	0·0001	0·04		
Men, all treatment groups, sudden death								
RR	1·47	NS	2·65	3·14	1·29†	NS	NS	Propranolol versus control, NS Bendrofluazide versus control, NS
95% CI	1·19–1·81		1·72–4·08	1·56–6·33	1·10–1·51			
p value	0·0012		<0·0001	0·0014	0·0015			

*Uses mean in-trial value †Uses entry values

‡$1_{1-2}4_{1-3}5_{1-2}$, one or more codes present.

¶The p value for each of these pressures is that for the inclusion of one factor before the other in a stepwise procedure; the CIs (confidence intervals) are calculated from the *t* values from the model containing both pressures

SBP, systolic blood pressure, DBP, diastolic blood pressure such as cigarettes smoked and the concentration of serum cholesterol were used without being categorised (for example smoker/non-smoker) as was done in a previous paper[1]—that is they were used as continuous variables. Also, where appropriate, where repeated measurements of a risk variable were available throughout the trial the mean of these in-treatment values was used, including for example the mean number of cigarettes smoked and the mean cholesterol concentration. We used entry values for age and for evidence of ischaemia in the electrocardiogram. In the previously published analysis body mass index at entry seemed to be a significant risk factor for coronary events.[1] Though there is some suggestion that body mass index may be a significant variable for sudden death in women, for men the effects of body mass index in the current analysis, using the averaged and non-categorised risk variables described above, are not significant. A further limitation of previous analysis (that has now been overcome) was that the relative risks could not be obtained simultaneously from a single logistic regression model. These differences in technique presumably account for the changed significance of body mass index.

Table 2 includes the results for all coronary events on the placebo. The pressure variable used is the mean in-trial value, which best characterises prevailing pressure during the period of observation. Both systolic and diastolic pressure are significant risk factors and the relative risks presented are for each pressure individually. For actively treated patients, pressures either at entry or in-trial were no longer significant risk factors.

Table 3 *Coronary events by presence or absence of risk factor at entry (totals may be smaller than the overall total, because data on presence or absence of the risk factor were sometimes missing)*

	Bendrofluazide		*Propranolol*		*Placebo*	
	No	*Rate*	*No*	*Rate*	*No*	*Rate*
Men						
Non-smokers	56	7·4	39	5·0	116	7·5
Smokers	43	12·7	45	13·8	83	12·6
No ischaemic ECG	91	8·9	74	7·0	173	8·4
Ischaemic ECG*	8	13·3	11	15·2	27	21·6
Serum cholesterol < 6·5 mmol/l	40	6·3	40	6·2	103	7·8
Serum cholesterol ≥ 6·5 mmol/l	54	13·2	44	10·1	93	11·2
Age 35–44 yr	11	4·4	10	3·9	17	3·3
Age 45–54 yr	33	6·9	39	8·0	83	8·7
Age 55–64 yr	55	14·9	36	9·6	100	13·4
Entry SBP (mm Hg)						
< 150	26	7·7	22	6·0	40	6·0
150–159	18	7·7	20	7·6	41	8·3
160–169	20	8·6	12	5·6	43	9·6
170–179	17	10·0	22	12·8	39	11·7
≥ 180	18	12·5	9	5·9	37	11·7
SBP (mm Hg) at 6/12:						
< 125	14	6·7	15	7·6	7	5·0
125–134	29	10·2	14	5·4	21	6·0
135–144	24	9·9	16	6·8	26	5·4
145–154	9	6·6	10	6·4	41	9·0
≥ 155	12	13·3	21	12·7	77	12·5
Women						
Non-smokers	6	0·8	6	0·8	15	1·0
Smokers	14	5·1	12	4·5	19	3·5
No ischaemic ECG	17	1·8	17	1·8	31	1·6
Ischaemic ECG*	3	3·3	1	1·2	3	2·2
Serum cholesterol < 6·5 mmol/l	3	0·8	6	1·6	8	1·0
Serum cholesterol ≥ 6·5 mmol/l	17	3·0	11	1·9	25	2·0
Age 35–44 yr	1	0·6	1	0·6	1	0·3
Age 45–54 yr	7	1·7	5	1·2	9	1·1
Age 55–64 yr	12	2·6	12	2·6	24	2·6
Entry SBP (mm Hg)						
< 150	4	2·8	1	0·5	3	1·0
150–159	1	0·5	2	1·0	7	1·8
160–169	9	4·0	1	0·4	6	1·4
170–179	2	1·0	4	1·8	6	1·4
≥ 180	4	1·5	10	4·7	12	2·3
SBP (mm Hg) at 6/12:						
< 125	4	1·6	2	1·2	1	0·4
125–134	5	2·0	0	0·0	4	1·3
135–144	5	2·3	2	0·8	7	1·7
145–154	2	1·3	4	2·4	10	2·4
≥ 155	4	5·5	4	4·1	9	1·4

*$1_{1-2}4_{1-3}5_{1-2}$ one or more code present.

Table 2 also shows the relative risks for sudden death for all treatments. Entry pressure was used because it is not confounded with treatment effect (as in-trial pressure would be), and in fact the entry pressure does seem genuinely to have more predictive power for sudden death than in-trial pressure. The principal difference between the relative risks for all coronary events and sudden deaths is for serum cholesterol, which was not a significant risk factor for sudden death.

SUBGROUPS DIVIDED BY STRENGTH OF RISK FACTOR (TABLE 3)

With few exceptions that may be attributable to the small numbers of events in some subgroups, event rates rose with the strength of the risk factor in both actively treated groups as well as in people on placebo. (Although selection for the trial was based on diastolic pressure, in keeping with the emphasis placed on diastolic pressure in clinical practice, there is general agreement that systolic pressure is more strongly associated with the risk of coronary disease. Since the purpose of this section is to display event rates in terms of the main risk factors, systolic pressures have accordingly been used.)

The small reduction in coronary event rates associated with propranolol treatment in men was restricted to non-smokers, in whom the rate in the treated group (5·0 per thousand person-years) was 33% less than that in the placebo group (7·5 per thousand person-years) ($p = 0·04$). In smokers given propranolol, treated and placebo rates were similar (13·8 and 12·6 per thousand person-years respectively). In a logistic regression analysis, however, an interaction analysis of treatment and smoking was not statistically significant ($p = 0·11$).

Further, to investigate whether there was a dose-response relation between the number of cigarettes smoked and the possible benefit associated with propranolol treatment, an on-treatment analysis was performed in which events were counted against the drug being taken when they occurred rather than that given at the time of randomisation, and smoking habit was categorised from cigarette consumption as recorded at the pre-event annual examination rather than at entry (table 4). The event rate did not consistently increase with the number of cigarettes smoked in any of the treatment groups. Both in the bendrofluazide and propranolol groups the rate in the non-smokers exceeded that in light smokers, and in the placebo group the rate in intermediate smokers was greater than that in men smoking 20 or more

Table 4 *Relation between number of cigarettes smoked, as recorded at the last annual examination before the event, and treatment in men—with analysis by treatment categorisation, not as randomised*

	Number of cigarettes smoked and coronary event rate					
	Bendrofluazide		*Propranolol*		*Placebo*	
	No	*Rate*	*No*	*Rate*	*No*	*Rate*
Non-smokers	49	8·2	35	5·6	94	7·7
Cigarettes/day:						
1–9	2	4·0	2	4·7	7	9·9
10–19	10	14·2	7	11·2	21	16·2
⩾ 20	19	17·0	19	17·1	29	14·0
	Difference between event rates in treated groups compared with placebo group (%)					
Non-smokers	+ 6		−27			
Cigarettes/day.						
1–9	−60		−52			
10–19	−12		−31			
⩾ 20	+21		+22			

Table 5 *Serum potassium (mmol/l) pre-event (sudden death) and in all subjects at first annual examination*

	Pre-sudden death			*First annual examination*		
	No	*Mean*	*SD*	*No*	*Mean*	*SD*
Bendrofluazide:						
Men	16	3·6	0·49	1988	3·6	0·49
Women	3	3·8	0·53	1829	3·5	0·50
Propranolol:						
Men	4	4·4	0·61	1999	4·2	0·41
Women	3	4·3	0·26	1844	4·2	0·44
Placebo·						
Men	22	4·1	0·80	3990	4·1	0·37
Women	2	4·2	0·00	3637	4·1	0·38

cigarettes daily. Analysis of the change in event rate by number of cigarettes smoked did not show a consistent trend within the propranolol group, where the percentage reduction was greater in light smokers than in the non-smokers. Only in the heaviest smokers was there no suggestion of benefit associated with propranolol treatment. The results in the bendrofluazide group, in which no overall benefit associated with treatment was suggested, were similar in that the rate in non-smokers was higher than that in the placebo group whereas that in light smokers was lower, and only in the heaviest smokers was there a clear excess of events in the treated group in comparison with the controls.

No specific hazard attached to bendrofluazide treatment when ischaemic changes were seen on the electrocardiogram at entry. Rates for men were 13·3 per thousand person-years in the bendrofluazide group compared with 15·2 on propranolol and 21·6 in the placebo group.

RELATION BETWEEN SERUM POTASSIUM CONCENTRATIONS AND SUDDEN DEATH (TABLE 5)

The mean concentrations of serum potassium (in an on-treatment analysis) at the anniversary examination preceding sudden death were compared with those in the complete treatment groups (as opposed to subgroups) at the first anniversary of entry. There were no significant differences, in any treatment regimen, between the concentrations in the sudden death category compared with those in all patients.

EVENT RATES BY DURATION OF TREATMENT (TABLE 6)

The apparent excess of coronary events occurring during the first year of follow up in men on bendrofluazide was caused by a difference in the sudden deaths category—there were six deaths in the bendrofluazide group compared with three in the placebo group which was twice the size of the bendrofluazide group. This excess was not statistically significant ($p = 0·08$). There were three non-sudden deaths in the first year on the diuretic compared with eight in the placebo group, and 16 non-fatal events on bendrofluazide compared with 32 on placebo; these results do not suggest any hazard associated with active treatment. There was no evidence of a trend in event rate with time on bendrofluazide. The postulated protective effect of propranolol was apparently greatest in the first year of treatment, but the difference between the strength of this possible effect in the first year and in other years was not significant.

EVENT RATES BY PULSE RATE AT ENTRY OR AT THE ANNUAL EXAMINATION PRECEDING THE EVENT (TABLE 7)

These results were inconsistent. In the placebo group, although pre-event pulse rate and event rate were apparently related, entry pulse rate and event rate were not. On bendrofluazide, entry pulse rate was possibly related to event rate, but pre-event pulse rate was not. On propranolol, pulse rate both at entry and at the pre-event measurement was possibly related to event rate.

Table 6 *Percentage event rates by year in trial* for men*

	Bendrofluazide		*Propranolol*		*Placebo*	
Event/time in trial	*No*	*%*	*No*	*%*	*No*	*%*
All coronary events*						
1st year	25	1·12	10	0·44	43	0·95
2nd year	19	0·86	18	0·80	39	0·88
3rd year	21	0·97	19	0·86	49	1·11
4th year	18	0·89	25	1·23	40	0·98
5th year	9	0·60	8	0·58	22	0·72
Fatal events*						
1st year	9	0·40	3	0·12	11	0·23
2nd year	8	0·36	8	0·36	17	0·38
3rd year	14	0·64	8	0·35	20	0·45
4th year	11	0·55	11	0·53	23	0·56
5th year	4	0·26	3	0·21	10	0·33
Sudden deaths*						
1st year	6	0·26	0	0·00	3	0·06
2nd year	3	0·13	4	0·18	13	0·29
3rd year	8	0·37	3	0·13	6	0·13
4th year	7	0·36	3	0·14	10	0·24
5th year	3	0·20	1	0·07	6	0·19

*Some events occurred after the fifth anniversary.

Table 7 *Coronary event rates (per 1000 person-years) by pulse rate (men)*

	Bendrofluazide		*Propranolol*		*Placebo*	
	No	*Rate*	*No*	*Rate*	*No*	*Rate*
Entry pulse rate (beats/min):						
<65	6	7·0	4	3·9	18	10·4
65–74	16	6·4	14	5·5	36	7·1
75–84	43	9·8	36	8·2	80	9·0
85–94	17	10·9	15	8·8	39	11·2
≥95	14	12·2	12	9·2	25	11·5
*Pre-event pulse rate (beats/min)**						
<65	13	9·2	17	4·8	20	8·1
65–74	19	7·1	26	8·3	43	8·1
75–84	43	9·8	29	9·5	85	9·4
85–94	16	10·4	10	11·7	32	9·3
≥95	8	8·8	3	5·5	20	11·9

*Pulse rate recorded at the anniversary examination preceding the event.

The rates in women were too low for subgroup analyses to be informative.

ELECTROCARDIOGRAPHIC ABNORMALITIES

Full details are shown in the tables, and only those points of particular interest with strong statistical significance will be described here.

The prevalence of major electrocardiographic abnormalities at entry was low and was closely similar in men and women, and in smokers and non-smokers (table 8). Treatment with bendrofluazide (tables 9 and 10) reduced the incidence of abnormally tall R waves in men and women ($p < 10^{-4}$) and increased the incidence of combined ST-segment and T-wave abnormalities in women ($p < 10^{-4}$). On propranolol, the incidence of T-wave inversion without ST segment changes was increased in women ($p < 10^{-4}$). When the data were divided by smoking habit (tables 11 and 12) these findings were less evident in smokers, possibly because these were the smaller groups. In men on propranolol, the frequency of combined ST-segment and T-wave abnormality was greater in smokers than in non-smokers ($p = 0·0001$).

There were considerable differences between the incidence of ventricular extrasystoles when the data were divided by sex, by treatment regimen, and by duration of follow up (table 13). There was no evidence that there was a trend with time in any treatment group or that the groups differed from one another in this respect.

Coronary events were more common in the group with any of the following abnormalities—major Q/QS abnormality, minor Q/QS abnormality, abnormally tall R waves, ST-segment depression, T-wave flattening or inversion, "strain" with tall R waves associated with ST-T abnormalities, ventricular extrasystoles totalling 10% or more of all recorded complexes—than in the group with normal electrocardiograms (relative risk 1·48, 95% confidence interval (CI) 1·17 to 1·86). Among the individual features, major abnormalities of the Q/QS waves (relative risk 2·29, CI 1·21 to 4·34), ST segment depression with T-wave inversion (relative risk 2·59, CI 1·43 to 4·71), T-wave inversion (relative risk 2·54, CI 1·53 to 4·23), and "strain" with tall R waves together with these ST-T manifestations (relative risk 3·49, CI 1·20 to 10·21), made statistically significant contributions. Minor Q/QS abnormalities, tall R waves in the absence of abnormal ST-T tracings, and ventricular extrasystoles totalling 10% or more of all recorded complexes were not statistically significant risk factors. "On treatment" analysis gave similar results.

COMPARISONS BETWEEN BENDROFLUAZIDE AND PROPRANOLOL

There are many occasions where, because the rates on the two drugs differ in opposite directions from that on the placebo, the between-drug comparisons show larger differences than do comparisons of the active drug with the placebo. These comparisons between drugs add little where the individual drug rates differ from the rates in the placebo group with a p value $<0·1$, since these more direct results could be used as the basis for a choice between drugs. For information, p values for between-drug differences none the less have been shown in all tables where they are $<0·1$. Not all will be enumerated here, but the following are of possible interest:

(*a*) *Sudden death in men (table 1)*—The rate on bendrofluazide was 2·6 per 1000 person-years, and that on propranolol was 1·1 per 1000 person-years (for the comparison of either of these rates with the rate in the placebo group of 1·8 per 1000 person-years $p > 0·1$). For the bendrofluazide compared with the

Table 8 *Percentage prevalence of major electrocardiographic abnormalities at entry (one person may appear more than once in this table). (Rates given per 100 entrants)*

	Men		*Women*	
	No	*Rate*	*No*	*Rate*
By sex:				
More definite abnormal Q/QS items compatible with infarction	118	1·3	128	1·5
Less definite changes suggesting infarction	184	2·0	163	2·0
Abnormally tall R waves	542	6·0	373	4·5
ST segment depressed or downward sloping, T wave inverted	114	1·3	146	1·8
LVH and strain	31	0·3	25	0·3
T wave inverted, ST segment normal	57	0·6	55	0·7
T wave minimally inverted or flat, ST segment normal	380	4·2	351	4·2
≥10% recorded complexes are ventricular extrasystoles	36	0·4	51	0·6

	S		*NS*		*S*		*NS*	
	No	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*
By smoking* (S, smokers; NS, non-smokers):								
More definite abnormal Q/QS items compatible with infarction	38	1·4	79	1·3	35	1·6	92	1·5
Less definite changes suggesting infarction	55	2·0	128	2·1	48	2·2	114	1·9
Abnormally tall R waves	137	4·9	402	6·5	62	2·8	309	5·1
ST segment depressed or downward sloping, T wave inverted	32	1·1	81	1·3	38	1·7	108	1·8
LVH and strain	8	0·3	23	0·4	4	0·2	21	0·3
T wave inverted, ST segment normal	15	0·5	41	0·7	13	0·6	42	0·7
T wave minimally inverted or flat, ST segment normal	129	4·6	250	4·1	103	4·7	246	4·1
≥10% recorded complexes are ventricular extrasystoles	7	0·2	29	0·5	22	1·0	29	0·5

	Men						*Women*					
	Bendrofluazide		*Propranolol*		*Placebo*		*Bendrofluazide*		*Propranolol*		*Placebo*	
	No	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*
By randomised regimen:												
More definite abnormal Q/QS items compatible with infarction	23	1·0	27	1·2	68	1·5	36	1·8	35	1·7	57	1·4
Less definite changes suggesting infarction	49	2·2	40	1·8	95	2·1	40	1·9	38	1·8	85	2·1
Abnormally tall R waves	120	5·4	146	6·4	276	6·1	87	4·2	91	4·3	195	4·7
ST segment depressed or downward sloping, T wave inverted	33	1·5	24	1·1	57	1·3	43	2·1	29	1·4	74	1·8
LVH and strain	9	0·4	6	0·3	16	0·4	5	0·2	5	0·2	15	0·4
T wave inverted, ST segment normal	9	0·4	15	0·7	33	0·7	14	0·7	16	0·8	25	0·6
T wave minimally inverted or flat, ST segment normal	90	4·0	111	4·9	179	4·0	90	4·4	105	5·0	156	3·8
≥10% recorded complexes are ventricular extrasystoles	8	0·4	9	0·4	19	0·4	12	0·6	14	0·7	25	0·6

*Totals are not always the same as in the other two parts of the table because in a small number of people the smoking habit at entry was unknown.

LVH, left ventricular hypertrophy.

propranolol rate, however, $p = 0{\cdot}01$.

(*b*) *Major Q/QS changes in women (table 9)*—On bendrofluazide the rate was 13·5 per 1000 person-years, compared with 9·8 per 1000 person-years on propranolol ($p = 0{\cdot}04$).

(*c*) *Tall R waves (table 9)*—In men the rate per 1000 person-years on bendrofluazide was less than that on propranolol (14·2 *vs* 18·2, $p = 0{\cdot}05$); in women the respective rates per 1000 person-years were 9·3 *vs* 15·6 ($p = 0{\cdot}0005$).

(*d*) *Ventricular extrasystoles amounting to > 10% of all complexes in men (table 9)*—For bendrofluazide the rate was 6·7 per 1000 person-years, similar to the placebo rate of 6·4 per 1000 person-years. For propranolol the rate was 4·5 per 1000 person-years, $p = 0{\cdot}08$ compared with the placebo group. For the bendrofluazide *vs* the propranolol rate, $p = 0{\cdot}08$.

Discussion

The frequency of coronary heart disease in this population corresponds well with that in other comparable series, with coronary event rates close to those in the Australian study[3] and the Oslo trial.[9] As with any trial, the results are strictly applicable only to the study population. We cannot be certain that

Table 9 *Incidence of major electrocardiographic (ECG) abnormalities during follow up (numbers and rates per thousand person-years)*

	Men						*Women*					
	Bendrofluazide		*Propranolol*		*Placebo*		*Bendrofluazide*		*Propranolol*		*Placebo*	
ECG abnormality	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*
Major Q/QS abnormalities	109	13·2*	84	9·8†	169	10·0	105	13·5	78	9·8†	190	12·1
Minor Q/QS abnormalities	80	10·3	59	7·2†	135	8·5	73	10·0	57	7·5°	148	10·1
Tall R waves	113	14·2***	146	18·2*•	367	23·3	71	9·3***	121	15·6°	283	18·9
ST depression, T-wave inversion	82	9·8	62	7·1**•	194	11·4	145	19·0***	91	11·4†††	172	10·8
LVH and strain	16	1·9	16	1·8	46	2·6	8	1·0*	15	1·8	41	2·5
T wave inverted, ST segment normal	32	3·9*	59	7·0†	109	6·7	46	6·4*	81	10·6††***	60	3·9
T wave flat or minimally inverted, ST segment normal	128	17·8**	148	19·8*	363	24·9	180	30·6*	168	26·3	332	25·4
Ventricular extrasystoles ⩾ 10% of recorded complexes	57	6·7	40	4·5°•	110	6·4	49	6·1	39	4·7	80	4·9

°p < 0·1; *p < 0·05; **p < 0·01; ***p < 0·001; for comparison of rate in actively treated group against placebo.
•p < 0·1; †p < 0·05;††p < 0·01, †††p < 0·001; for comparison of rate in one actively treated group with the other.

the findings would have been identical in a group characterised, for example, by a higher proportion of smokers or by less of a tendency towards a spontaneous decline in blood pressure from entry levels, but it seems unlikely that they would be qualitatively different.

Drug treatment had no effect on the rate of coronary heart disease overall and, although there are suggestions in the present data that both the active drugs may have been associated with benefits, the results must be interpreted with great care. If true, the suggestion that propranolol reduced the attack rate of coronary events in male non-smokers would be of considerable importance, but our data are

Table 10 *Reversion rates of major electrocardiographic (ECG) abnormalities during follow up (numbers and rates per thousand person-years)*

	Men						*Women*					
	Bendrofluazide		*Propranolol*		*Placebo*		*Bendrofluazide*		*Propranolol*		*Placebo*	
ECG abnormality	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*
Major Q/QS abnormality	18	455·9	20	465·1	47	365·4	27	651·6	31	500·0	46	598·8
Minor Q/QS abnormality	36	690·0	27	467·6	63	563·6	29	537·0	26	520·0	62	632·6
Tall R waves	96	440·7°	111	502·4**	195	354·3	62	427·7	63	364·2	137	344·6
ST-T abnormalities	23	465·6	15	333·3	33	363·8	36	432·9	21	416·8	55	458·4
Strain	7	777·8	5	454·5	13	722·2	5	714·3	5	625·0	13	565·2
T wave inverted, ST segment normal	8	888·9	9	409·1	22	628·6	11	846·1	10	476·2	16	666·7
T wave flat or minimally inverted, ST segment normal	64	606·2	78	705·6	104	656·2	61	681·3	70	719·7	107	681·7
Ventricular extrasystoles ⩾ 10% of all recorded complexes	7	583·3	9	900·0	17	772·7	11	647·1	10	512·7	22	709·7

°p < 0·1 and **p < 0·01 for comparison of rates in actively treated group against placebo.
None of the comparisons of rates in one actively treated group with the other is significant even at the p < 0·1 level.

Table 11 *Incidence of electrocardiographic (ECG) abnormalities by smoking habit (rates per 1000 person-years)*

	Men						*Women*					
	Bendrofluazide		*Propranolol*		*Placebo*		*Bendrofluazide*		*Propranolol*		*Placebo*	
ECG abnormality	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*
Major Q/QS abnormality												
S	29	12·1	25	10·6	54	11·2	33	16·8	14	7·1°	49	12·3
NS	79	13·7*	58	9·4	115	9·6	72	12·4	64	10·7	140	12·0
Minor Q/QS abnormality												
S	20	8·9	16	7·0	42	9·3	18	9·5	16	8·5	45	12·1
NS	59	11·0°	43	7·3	93	8·1	55	10·1	41	7·2	102	9·4
Tall R waves												
S	33	13·8**	38	16·5°	108	23·4	13	6·6**	22	11·3	67	17·2
NS	80	14·6***	107	19·1°	257	23·1	58	10·3***	99	17·1	214	19·4
ST-T abnormalities												
S	30	12·2	33	13·8†††	64	13·6	30	15·3	28	14·3	55	13·7†
NS	49	8·3	29	4·6***	128	10·4	115	20·4***	63	10·6	116	9·8
Strain												
S	5	2·0	5	2·0	15	3·1	1	0·5	3	1·5	9	2·2
NS	11	1·8	11	1·7	30	2·4	7	1·2°	12	1·9	32	2·6
T wave inverted, ST segment normal												
S	11	4·5°	23	9·9	39	8·3	12	6·4	21	11·3*	19	5·0
NS	21	3·7°	35	5·7	69	5·9	34	6·4*	59	10·2***	40	3·6
T wave flat or minimally inverted, ST segment normal												
S	39	18·4**	47	23·9	125	31·3††	44	28·2	32	21·0	92	27·3
NS	89	17·6°	99	18·2°	237	22·5	136	31·6*	136	28·1	238	24·4
Ventricular extrasystoles ≥ 10% of recorded complexes												
S	17	6·7	15	6·0	33	6·7	15	7·3	12	6·1	25	6·3
NS	40	6·7	25	4·0°	77	6·2	34	5·8	27	4·4	55	4·6

°p < 0·1; *p < 0·05; **p < 0·01; ***p < 0·001; for comparison of rates on either active drug with rates on placebo.
†p < 0·05; ††p < 0·01, †††p < 0·001; for comparison of rates in smokers with rates in non-smokers.
S, smokers; NS, non-smokers.

inconclusive. An analysis of the interaction between the type of treatment and smoking in determining coronary events did not give a statistically significant result ($p = 0{\cdot}11$) and although the putative effect was proportionally large, with about one third of events saved, the difference between event rates in the propranolol and placebo groups was only just statistically significant ($p = 0{\cdot}04$).

The absence of a convincing dose-response relation in the present data between the number of cigarettes smoked daily and the percentage reduction in the coronary event rate in men on propranolol also serves to reduce the credibility of the postulated effect, and we now reiterate and re-emphasise the caution expressed in our first paper[1] about the interpretation of post hoc subgroup findings. The theory, however, receives some support from the independent finding in the International Prospective Primary Prevention Study in Hypertension of a similar effect in a group treated with oxprenolol.[6] It is known that the antihypertensive action of propranolol differs between smokers and non-smokers, and other drug effects might be similarly modified by smoking.[10]

Active treatment had a beneficial effect on the electrocardiographic changes thought to be caused by cardiac hypertrophy, both in reducing their incidence (in accord with other published work[11]) and in increasing the proportion reverting to normal. The factors modulating the reversal of such electrocardiographic changes are clearly complex,[12 13] and are not restricted to changes in blood pressure, for in our results as in other published work[14] the comparative efficacy of the two drugs in this respect differs from that of their antihypertensive action.[1]

The decreased occurrence of repolarisation abnor-

Table 12 *Reversion of electrocardiographic (ECG) abnormalities by smoking habit (rates per thousand person-years)*

	Men						*Women*					
	Bendrofluazide		*Propranolol*		*Placebo*		*Bendrofluazide*		*Propranolol*		*Placebo*	
ECG abnormality	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*
Major Q/QS abnormality												
S	6	313 7	7	437 5	14	359 0	7	700 0	7	636·4	12	625·2
NS	12	545 2	12	461 5	33	393 9	20	623 1	24	470 6	34	629·6
Minor Q/QS abnormality												
S	10	666 7	7	500 0	19	638·5	9	486 0	9	428 6	16	468·7
NS	26	722 2	19	387·8	44	569 4	20	526·3	17	586 2	46	676 5
Tall R waves												
S	29	513·8	26	587 3	53	405·3	10	434·8	12	428 6	18	304 2
NS	65	410 7	85	491 7	142	347·0	52	424·6	50	347 2	118	352·1
ST-T abnormalities												
S	4	444·4	4	571 4	9	236·8	12	463·8	4	333 3	12	600·0
NS	19	450 4	11	289 5	24	395·7	24	421·0	17	485 3	43	412·9
Strain												
S	1	1000 0	1	1000 0	5	833·3	2	666 7	1	1000 0	0	0 0
NS	6	750 0	4	400 0	8	666 7	3	750·0	4	571 4	13	565 2
T wave inverted, ST segment normal												
S	2	1000 0	4	571 4	4	1000 0	4	1000·0	3	750·0	4	571 4
NS	5	274 8	5	333·3	18	580 6	7	777·8	7	411·8	12	705·9
T wave flat or minimally inverted, ST segment normal												
S	18	476 5	24	705·9	38	614 7	20	833 3	25	660·4	25	714 3
NS	46	682·6	54	709·5	66	707 0	41	624·7	45	789 5	82	664 9
Ventricular extrasystoles ≥ 10% of recorded complexes												
S	1	1000 0	2	1000 0	4	666 7	6	857·1	5	714·3	7	538·5
NS	6	545 4	7	875 0	13	812 5	5	500·0	5	500 0	15	833 3

S, smokers; NS, non-smokers.
No differences between rates in drug groups compared with the placebo group, or in the active drug groups compared with one another, were significant even at the p < 0 1 level.

malities in men on bendrofluazide shown here has been reported before[11] but (to our knowledge) the difference between the sexes, with an increased rate in women, has not. The reason for this sex difference is unclear. Repolarisation abnormalities are associated with reduced concentrations of serum potassium, but the potassium-lowering effect of bendrofluazide was similar in men and women.[15]

Our data do not unequivocally confirm the suggestion made in the report on the MRFIT study that thiazide diuretics might increase the rate of coronary heart disease mortality in men with baseline resting

Table 13 *Incidence of ventricular extrasystoles* by year of follow up*

	Men						*Women*					
	Bendrofluazide		*Propranolol*		*Placebo*		*Bendrofluazide*		*Propranolol*		*Placebo*	
Time in trial	*No*	*Rate***	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*
Entry to 1 year	19	9·3	10	4·8	22	5·3	13	6 9	10	5 2	13	3·4
1–2 years	12	6 2	8	4·0	23	5·9	14	7·9	9	4·9	22	6 1
2–3 years	14	7 7	7	3 7	28	7·5	8	4·7	6	3 4	12	3 5
3–4 years	10	5 9	5	2 9	25	7·4	8	5 0	7	4 3	19	6 0
4–5 years	2	1 7	10	8 0	12	5 0	6	5 0	7	5 8	14	6·0

*Totalling ≥ 10% of all recorded complexes (Minnesota code 8_1(V)).
**Rate per 1000 person-years.

Table 14 *Relation between electrocardiographic (ECG) abnormalities and the occurrence of clinically evident coronary events*

	Men						*Women*					
	Bendrofluazide		*Propranolol*		*Placebo*		*Bendrofluazide*		*Propranolol*		*Placebo*	
ECG abnormality	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*
						Coronary events, fatal and non-fatal						
Major Q/QS abnormality												
Present	7	30 9*	5	24 3	10	23·4**	0	0 0	1	4 4	0	0 0
Absent	92	9 4	80	7·9	190	9·5	20	2·2	17	1·8	34	1·8
Minor Q/QS abnormality												
Present	4	17 4	2	11 7	11	26 4**	1	6 9	2	11 6†	1	2·1
Absent	88	9 1	78	7 8	179	9 2	19	2 1	15	1·6	33	1·8
Tall R waves												
Present	5	10 4	4	7·8	16	11 9	1	2·8	2	4 6	1	0·7
Absent	94	9 8	81	8 3	184	9·7	19	2·1	16	1 8	33	1 9
ST-T abnormalities												
Present	5	19 5	5	43 8***	16	23 1**	1	3 0	2	7·3	1	3·7
Absent	94	9 5	80	7·9	184	9 2	19	2 1	16	1·7	33	1·8
Strain												
Present	0	0 0	0	0 0	1	7·1	0	0·0	0	0 0	0	0 0
Absent	99	9 9	85	8 2	199	9 8	20	2·1	18	1 9	34	1·8
T wave inverted, ST segment normal												
Present	2	32 2	2	16·7	3	16·4	0	0 0	2	13·2*	0	0 0
Absent	92	9·4	78	7 7	181	9·2	19	2·1	14	1 5	33	1 8
T wave flat or minimally inverted, ST segment normal												
Present	9	22 0*	3	6·8	21	21 7***	1	1·9	1	3·3	1	1·0
Absent	81	8·7	72	7 6	148	8 1	17	2·1	11	1 3	28	1 6
Ventricular extrasystoles ≥ 10% of all recorded complexes												
Present	4	49 4*	0	0 0	3	15 7	0	0 0	0	0 0	1	9 5
Absent	95	9 5	85	8·2	197	9·7	20	2 1	18	1·9	33	1 7
						Fatal coronary events						
Major Q/QS abnormality												
Present	8○	34·2***	4	19 4**	9	17 2**	0	0 0	0	0 0	0	0 0
Absent	42	4 3	34	3 4	78	3·9	9	1·0	9	1 0	10	0 5
Minor Q/QS abnormality												
Present	2	8 9	2	11·7	5	13 0*	0	0 0	1	6 1	1	2 1
Absent	40	4·1	32	3 2	73	3 7	9	1 0	8	0 9	9	0 5
Tall R waves												
Present	1	1 9	2	3 4	8	5·8	1	2 8	1	2 7	1	0 7
Absent	49	5 1	36	3·7	79	4 2	8	0 9	8	0 9	9	0 5
ST-T abnormalities												
Present	4	12 7	5	43 8***	13	19 1***	0	0 0	0	0 0	1	3 7
Absent	46	4 7	33	3·2	74	3 7	9	1·0	9	0 9	9	0 5
Strain												
Present	0	0 0	0	0 0	1	7 1	0	0 0	0	0 0	0	0 0
Absent	50	5 0	38	3 7	86	4 2	9	1 0	9	0 9	10	0 5
T wave inverted, ST segment normal												
Present	1	22 5	1	10 2	3	11 6†	0	0 0	0	0 0	0	0 0
Absent	45	4 6	32	3 2	71	3 6	9	1 0	9	1 0	9	0·5

Table 14

	Men						*Women*					
	Bendrofluazide		*Propranolol*		*Placebo*		*Bendrofluazide*		*Propranolol*		*Placebo*	
ECG abnormality	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*	*No*	*Rate*
T wave flat or minimally inverted, ST segment normal												
Present	3	6 5	3	6·8	10	9·4**	0	0 0	1	3 3	0	0 0
Absent	39	4 2	26	2·7	54	2·9	9	1 1	7	0·8	7	0·4
Ventricular extrasystoles ≥ 10% of recorded complexes												
Present	5	56·9***	0	0 0	4	23 2**	0	0 0	0	0 0	0	0 0
Absent	45	4·5	38	3 7	83	4 1	9	1 0	9	0 9	10	0 5

°The number of fatal events shown in any one line may appear to exceed the number of fatal and non-fatal events combined if the ECG has changed between a non-fatal and a fatal event.

†p < 0 1; *p < 0 05; **p < 0 01; ***p < 0 001; for comparison of rate with ECG abnormality present against rate in group without abnormality.

electrocardiographic abnormalities.[4] The MRFIT results may have been distorted by the anomalous finding in the control group of lower mortality from coronary heart disease in men with abnormal electrocardiograms than in those with normal electrocardiograms. In the present results it was clear that the presence of major electrocardiographic abnormalities was associated with an increased likelihood of having a clinical event, but there was no evidence that this relation, whether for all events or for fatal events only, was strengthened by bendrofluazide treatment.

There are none the less certain aspects of our results that need careful assessment with respect to the postulated adverse effect associated with bendrofluazide treatment. These include the finding, noted early in the study, of an excess of sudden deaths in men in the thiazide group compared with those on placebo. This excess, small and not statistically significant, did not justify changing the protocol or stopping the trial. Two substudies were then set up to try to detect adverse effects possibly associated with the rather high (10 mg daily) dose of bendrofluazide. In one, the antihypertensive efficacy of, and adverse reactions to, two doses of bendrofluazide were compared.[16] In the second, the relation between thiazide treatment and ventricular extrasystoles was examined, and showed an increase in the occurrence of ventricular extrasystoles in the first year of bendrofluazide treatment which was not maintained subsequently.[17]

The sudden death rate was slightly, though not statistically significantly, increased on bendrofluazide compared with placebo. There was a slight increase in major Q/QS abnormalities in men on bendrofluazide (p = 0·03 compared with the placebo group). The rates of coronary events on bendrofluazide in the presence of major Q/QS abnormalities or a high frequency of ventricular extrasystoles were increased, though not statistically significantly so. Taken singly, none of these findings has great weight. When all are considered together, although our data do not definitely support the suspicion raised in the MRFIT report, neither do they refute it.

As well as information about clinical events, this study gave considerable information on electrocardiographic changes. The frequency and reversion of these abnormalities were defined as the first recorded change in an individual, whatever alterations occurred subsequently—a simple way of handling the data but one which will to some extent have inflated the figures. Other work, however, describes higher rates for reversion even of Q waves,[18 19] so our approach may not have greatly exaggerated the results, and is free of apparent bias. Each treatment used in the trial may, however, in different ways, have altered the relation of electrocardiographic findings to clinical disease, and made interpretation difficult. Taken as a whole, the most interesting aspect of the electrocardiographic findings is the difference between the results for Q/QS changes in "silent" infarctions, and those for clinically evident coronary events. The incidence of the former differed little between men and women or between smokers and non-smokers, contrasting strongly with the results for clinical episodes, and the possible protective effect of propranolol against coronary events in non-smokers was not evident against the electrocardiographic changes. Factors other than myocardial ischaemia which predispose to the development of clinical manifestations of infarction may be more common in men than in women and more in smokers than in non-smokers, and the putative protective effect of propranolol could be exerted against one of these factors.

These results are tantalising. They include two suggestions of benefit associated with propranolol and of hazard associated with bendrofluazide which, if substantiated, would be of considerable importance but which even a study of this size fails conclusively to demonstrate. These findings alone are difficult to use as a basis for decisions about the choice of drug treatment for mild hypertension and should be considered together with those for the effects of treatment on the stroke rate[1] which are shortly to be presented in more detail with fuller information for subgroup analyses.

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Prolonged QT period in diabetic autonomic neuropathy: a possible role in sudden cardiac death?

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SUMMARY Twenty four men with insulin dependent diabetes and different degrees of autonomic neuropathy were studied to establish the response of the QT interval to various heart rates. Nine men with autonomic neuropathy had a longer QT interval than 13 healthy individuals and 15 patients who had diabetes without, or with only mild, autonomic neuropathy. Those with autonomic neuropathy also had a proportionally greater lengthening of the QT interval for a given increase in RR interval.

The results of this study suggest a basis for the finding that sudden death is more common in patients with diabetic autonomic neuropathy.

An association between an abnormal QT interval and sudden cardiac death has been found in various diseases.[1 2] The influence of autonomic tone on the QT period is also widely accepted, although the mechanisms underlying the shortening or lengthening of this period are still not clear.[3 4]

In the late 1970s several reports noted the high incidence of sudden death in diabetic patients who had severe autonomic neuropathy.[5 6] In some cases death was attributed to cardiorespiratory arrest, but in the overwhelming majority the cause of death was not identified.

This prompted us to investigate changes in QT interval during static (quiet lying, sitting, and standing) and dynamic (Valsalva manoeuvre) conditions in groups of diabetic patients with different degrees of autonomic neuropathy.

Patients and methods

The diabetic patients (men aged (mean (SD)) 42 (12)) were subdivided into three groups: eight without autonomic neuropathy, seven with borderline autonomic neuropathy, and nine with definite autonomic neuropathy confirmed by their cardiovascular response to a series of autonomic tests (Valsalva manoeuvre, deep breathing, change of position from lying to standing, sustained hand grip, fall in blood pressure on standing) recommended by Ewing *et al*[7] and scored by a specially devised system.[8] All the patients had been admitted to the ward for tests to evaluate metabolic control and complications. Their metabolic control was acceptable (glycosylated haemoglobin mean (SD) value = 9·2 (1)% and their electrolyte balance (sodium, potassium, chloride, calcium, phosphorus, and magnesium) was within the normal range. None had electrocardiographic evidence of, or a history of, cardiovascular disease. The control group consisted of 13 healthy men aged 37 (8) years.

METHODS

Electrocardiograms were recorded at 25 mm/s. The QT and RR intervals were measured on a three channel ECG trace over a randomly selected segment of ten beats after three periods of at least two minutes of lying, sitting, and standing. For each position we took the mean of three similar beats in the three recordings as the baseline values. QT and RR intervals were then measured in each subject during three Valsalva manoeuvres at maximum tachycardia induced on forced expiration (phase 2) and maximum bradycardia after expiration (phase 4). We calculated the mean of three values obtained for each heart rate. The Valsalva manoeuvres were performed in standardised conditions—that is by blowing into a dynamometer for 15 seconds at 40 mm Hg.[9] The Valsalva ratio was calculated (longest RR in phase 4: shortest RR in phase 2). The QT interval was measured carefully according to the guidelines of Simonson *et al.*[10] We calculated the corrected QT interval (QTc) for each heart rate by Bazett's formula ($QTc = QT/\sqrt{RR}$).

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STATISTICAL ANALYSIS

We used Student's tests for paired and unpaired data. Analysis of covariance was applied to the regression slopes between QT (dependent variable) and RR (covariate) for the four groups studied. We used program P1V of the Biomedical Computer Programs statistical package for these calculations.[11]

Results

STATIC ANALYSIS

Figure 1 shows that the QT interval during quiet sitting, even when uncorrected for heart rate, was significantly longer in diabetic patients with autonomic neuropathy than in healthy individuals (360 (30)) ms *vs* 340 (10) ms, $p < 0·05$ when the RR interval was 750 (90) ms *vs* 824 (80) ms respectively (NS). During quiet standing the QT interval was significantly longer in diabetic patients with autonomic neuropathy than in those without autonomic neuropathy (350 (20) ms *vs* 320 (30) ms ($p < 0·05$)) when the RR interval was 751 (100) ms *vs* 712 (78) ms respectively (NS) and in the controls QT 320 (10) ms ($p < 0·01$) when the RR interval was 770 (100) ms (NS). Figure 1, however, also shows that in all cases the QTc interval was significantly longer in diabetic patients with autonomic neuropathy than in those without and in controls during lying, sitting, and standing.

DYNAMIC ANALYSIS

Figure 2 shows the distribution of QT values in relation to RR values for each group examined at rest, maximal tachycardia of phase 2, and maximal bradycardia of phase 4 during the Valsalva manoeuvre. Linear regression analysis of the distribution of QT and RR values in all groups gave the regression equation $y = bx + a$. The regression coefficient for the diabetic patients with autonomic neuropathy ($b = 0·22$, $a = 193$, $r = 0·824$) was significantly different from that of the diabetic patients without autonomic neuropathy, with borderline autonomic neuropathy, and controls ($p < 0·0001$). Regression coefficients in the last three groups were not significantly different from one another ($b = 0·086$, $a = 260$, $r = 0·807$; $b = 0·107$, $a = 253$, $r = 0·881$; and $b = 0·083$, $a = 272$, $r = 0·815$ respectively).

As expected fig 2 shows that the variation of RR intervals was lower in diabetic patients with autonomic neuropathy (mean Valsalva ratio 1·18 (0·10)) (table). The difference between the slope of the diabetic patients with autonomic neuropathy was

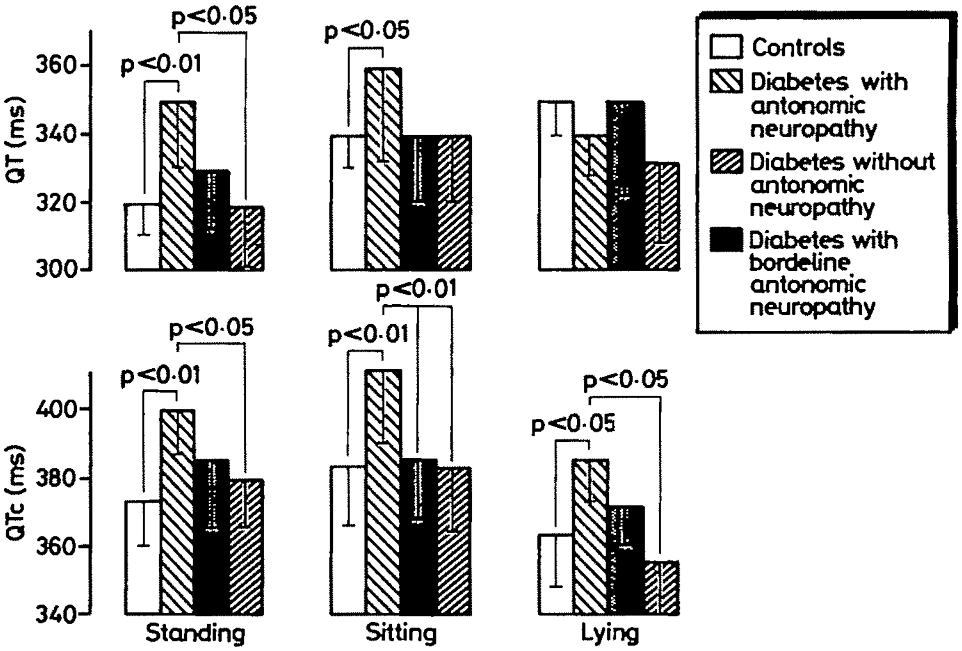

Fig 1 *Mean values (ms) for QT and QTc intervals during quiet standing, sitting, and lying in 13 controls, nine diabetic patients with autonomic neuropathy, seven diabetic patients with borderline autonomic neuropathy, and eight diabetic patients without autonomic neuropathy.*

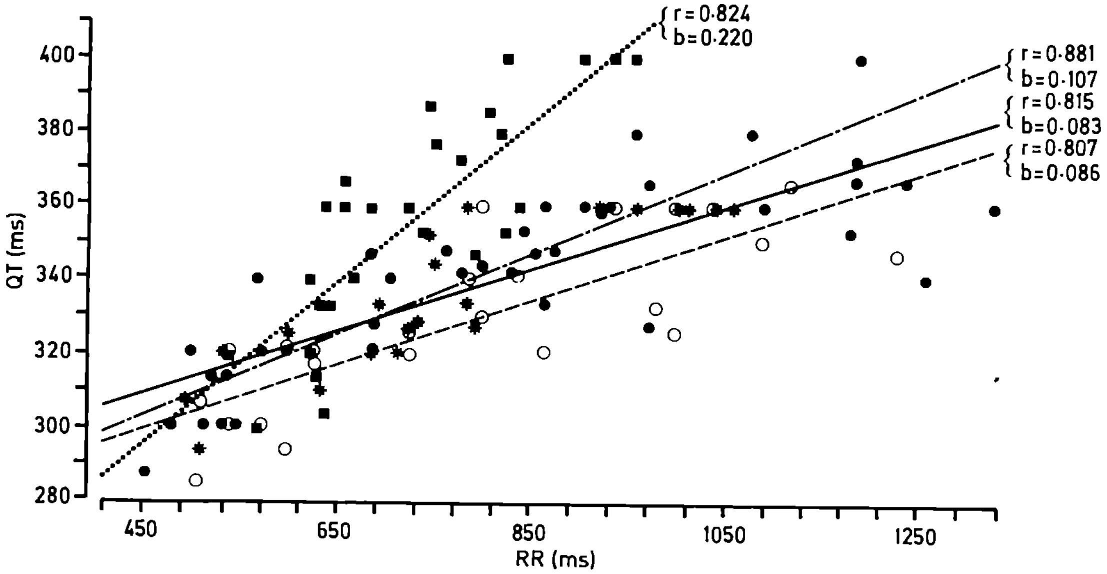

Fig 2 *Regression lines for mean individual QT vs RR intervals in phase 2, resting, and phase 4 of Valsalva manoeuvre in 13 controls (●——●), eight diabetic patients without autonomic neuropathy (○– – –○), seven diabetic patients with borderline autonomic neuropathy (*–·–·–*), and nine diabetic patients with autonomic neuropathy (■. .■). b, regression coefficient; r, correlation coefficient.*

highly significant (F = 9·02, $p < 0·0001$) from the cumulative slope of the other three groups (fig 3).[11] These three groups may be viewed as having a common regression line (b = 0·088; a = 265, r = 0·814) because there was no significant difference (F = 0·80) between their individual regression lines.

Discussion

The data clearly show that the relation between QT and RR intervals is altered under both static and dynamic conditions in diabetic patients with overt autonomic neuropathy. The importance of the autonomic influence in determining the QT interval is well established.[3 4 12] Because there was no other apparent cause to explain the abnormal lengthening of the QT interval in our diabetic patients with autonomic neuropathy, it seems reasonable to attribute this to a disturbance of the autonomic regulation of myocardial repolarisation.

The mechanism underlying this alteration is not easily explained. It is generally agreed that the parasympathetic system has little, if any, direct effect on QT modulation, which is widely attributed to

Table *Mean group values of RR and related QT intervals (ms) at maximum tachycardia (in phase 2) and at resting and maximum bradycardia (in phase 4) measured during three Valsalva manoeuvres in 13 controls, eight diabetic patients without autonomic neuropathy, seven diabetic patients with borderline autonomic neuropathy, and nine diabetic patients with autonomic neuropathy*

		Tachycardia		*Resting*		*Bradycardia*		
	No	*RR*	*QT*	*RR*	*QT*	*RR*	*QT*	*Valsalva ratio*
(a) Controls	13	554 (73)	315 (18)	824 (77)	344 (12)	1119 (132)	364 (18)	2·06 (0·37)
(b) Diabetes without autonomic neuropathy	8	562 (44)	305 (13)	812 (111)	337 (16)	1009 (115)	344 (18)	1·80 (0·28)
(c) Diabetes with borderline autonomic neuropathy	7	614 (110)	318 (14)	793 (137)	340 (19)	901 (139)	349 (18)	1·47 (0·30)
(d) Diabetes with autonomic neuropathy	9	660 (84)	347 (31)	750 (97)	358 (29)	779 (121)	365 (30)	1·18 (0·10)
			Significance testing					
a *vs* b		NS	—	NS	—	NS	—	NS
a *vs* c		NS	—	NS	—	<0·05	—	<0·005
a *vs* d		<0·01	—	NS	—	<0·001	—	<0·001
b *vs* c		NS	—	NS	—	NS	—	NS
b *vs* d		<0·01	—	NS	—	<0·005	—	<0·001
c *vs* d		NS	—	NS	—	NS	—	<0·05

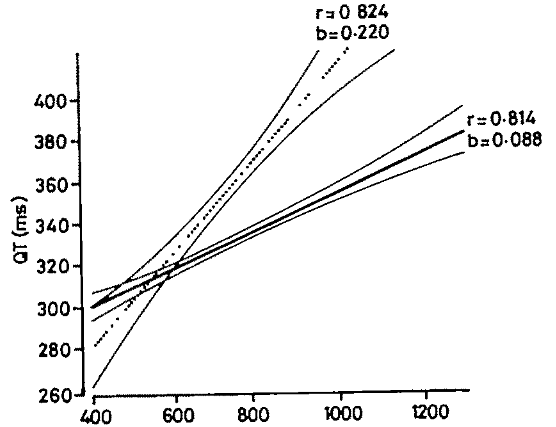

Fig 3 *Regression lines and confidence intervals for QT vs RR intervals during the Valsalva manoeuvre in nine diabetic patients with autonomic neuropathy (. . . . .) and in all the remaining subjects (————). b, regression coefficient; r, correlation coefficient.*

sympathetic influence[3 4] and recent evidence suggests that the left efferent cardiac sympathetic fibres may influence QT interval.[2]

In our patients it is difficult to propose a sound hypothesis for the effective mechanism underlying lengthening of the QT interval because diabetic patients with autonomic neuropathy show a pattern of overriding parasympathetic withdrawal followed by a sympathetic deficiency which at present is difficult to evaluate in clinical practice. Because the parasympathetic pathway does not appear to operate in these patients, we agree with recent reports that some non-quantifiable sympathetic imbalance is responsible for the abnormal lengthening of the QT interval in our patients. Evidence suggests that in diabetic patients with autonomic neuropathy the prolonged mean values for QT interval resemble (for example QT = 362 ms for an RR = 750 ms, that is QTc = 413 ms during quiet sitting) those found in patients with the so-called "long QT syndrome", a condition in which there is a high risk of sudden cardiac death.[2]

In the late 1970s there were several reports that unexpected sudden death was common in diabetic patients with autonomic neuropathy.[6 7] In some cases this was attributed to a respiratory arrest. But this was confirmed as the cause of death in only two cases and no explanation could be found for the remaining cases. Since then evidence has tended to argue against the hypothesis of simple respiratory arrest as the cause of death, because no alteration in the response to hypoxia or hypercapnia has been found in patients with autonomic neuropathy.[13 14]

Analysis of our data on QT adaptation to RR variation during dynamic conditions (fig 2) shows that the QT interval was similar in all diabetic patients and controls at the lowest values of RR (induced tachycardia) but that as the RR interval lengthened, the QT interval tended to increase proportionally more in patients with autonomic neuropathy until highly abnormal values of > 400 ms were reached when the RR interval was 1000 ms (heart rate = 60 beats/min).

There was a tendency towards tachycardia in the patients with diabetic autonomic neuropathy and none had a resting heart rate as low as 60 beats/min. But even in patients with autonomic neuropathy some interventions, such as drug treatment and anaesthesia, can lower the heart rate. Most sudden deaths in such patients occur during the induction of anaesthesia, which commonly provokes pronounced bradycardia, a condition which greatly increases the risk of cardiac arrest even in healthy subjects.[15]

In 1984 we suggested that the increase in QT interval that we found in diabetic patients with autonomic neuropathy might explain their high risk for sudden death.[16] The current study and another[17] support this view.

Should autonomic diabetic cardiac neuropathy be included among the long QT syndromes and could the altered relation between QT interval and RR interval in such patients explain the high incidence of sudden unexpected death in these patients? We hope that studies such as ours will lead to an answer.

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Case reports

Complete heart block after balloon dilatation for congenital pulmonary stenosis

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SUMMARY Permanent complete heart block developed in a five year old child during balloon dilatation for pulmonary valve stenosis. Damage to the atrioventricular node by pressure from the inflated balloon may have caused the conduction defect.

Percutaneous balloon dilatation has become an accepted non-surgical treatment for congenital pulmonary valve stenosis since it was introduced by Kan *et al* in 1982.[1] Recent reports on a large number of patients have demonstrated good results and few side effects.[2–4] The most important complications are systemic hypotension and arrhythmias during the dilatation process; both are transient and revert to normal spontaneously. No long term adverse sequelae have been reported. We describe a case in which permanent complete heart block developed during balloon dilatation.

Case report

A five year old girl who had had a heart murmur detected early in infancy was referred for investigation. She remained symptom free. Physical examination showed a normal girl with body weight 17 kg (50th percentile) and height 102 cm (50th percentile). The peripheral pulses were normal with a regular rate of 80/min and the blood pressure was 95/65 mm Hg. The heart was not enlarged but there was a strong cardiac impulse and a systolic thrill along the left sternal border. The first heart sound was normal, the second heart sound was split with a soft pulmonary component. A harsh grade 4/6 ejection systolic murmur was audible over the upper left sternal border. There was no ejection click. The lungs were clear and the liver was not enlarged. Chest *x* ray showed normal lung vascularity. Electrocardiogram showed sinus rhythm of 80 beats/min (fig 2a) and right ventricular hypertrophy. Cross sectional echocardiogram showed a thickened pulmonary valve with systolic doming. The peak systolic gradient across the pulmonary valve estimated by pulsed Doppler was about 60 mm Hg. Moderate pulmonary valve stenosis was diagnosed and written consent was obtained from her parents for cardiac catheterisation and balloon dilatation of the pulmonary valve.

The procedure was performed under general anaesthesia as recommended by some workers.[5] Intramuscular trimeprazine 30 mg was given as premedication one hour before the catheterisation. Intravenous ketamine 30 mg and atropine 0·1 mg were used for induction of anaesthesia and pancuronium bromide 1·5 mg for muscle relaxation. The patient was ventilated through a 5 mm uncuffed nasotracheal tube with a 3:2 mixture of nitrous oxide and oxygen and an expiratory minute volume of 2·8 l/min. A 7F balloon tipped end hole catheter was introduced by percutaneous puncture into the right femoral vein and was advanced to the left pulmonary artery. Sequential oxygen saturations and direct pullback pressure readings were obtained in the pulmonary artery, right ventricle, right atrium, and the vena cavae. The gradient across the pulmonary valve was 55 mm Hg and the right ventricular systolic pressure was 70 mm Hg. A 22 gauge cannula was inserted into the left brachial artery to monitor the systemic blood pressure. A 6F balloon tipped angiographic catheter was then introduced via the left femoral vein into the right ventricle and a cineangiogram was taken in the anteroposterior and

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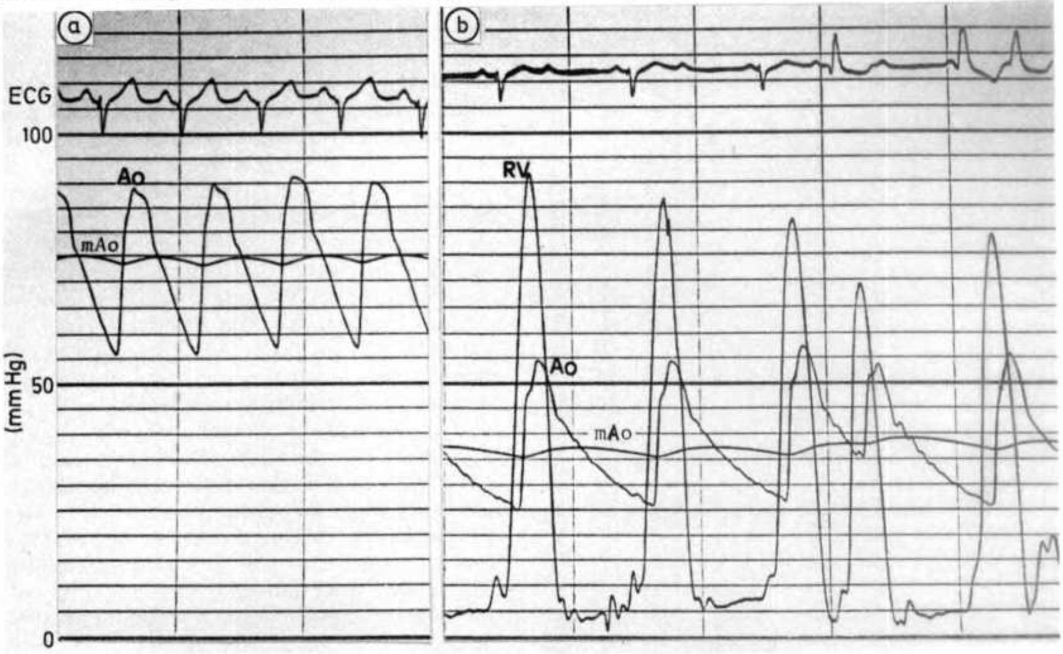

Fig 1 *(a) Electrocardiogram (ECG) and systemic arterial pressure (Ao) before balloon dilatation. (b) Electrocardiogram, systemic arterial (Ao), and right ventricular (RV) pressure during balloon inflation. mAo, mean systemic arterial pressure.*

the lateral projections. The diameter of the pulmonary valve annulus measured from videotape replay on the monitor using the external diameter of the catheter as the reference was 18 mm.

The end hole catheter was again advanced to the left lower lobe pulmonary artery and a 0·038 inch exchange guide wire was passed. The catheter and sheath were removed and a balloon dilatation catheter with a 20 × 40 mm balloon on a 9F shaft was inserted over the guide wire and advanced to the upper inferior vena cava. The balloon was flushed with a 1:1 mixture of physiological saline and contrast (meglumine iothalamate, Conray 280) to remove air bubbles. It was then advanced until its midportion was over the position of the pulmonary valve as marked on the fluoroscopic monitor. The balloon was rapidly inflated by hand until the indentation on the balloon produced by the stenotic pulmonary valve disappeared, and was then rapidly deflated and withdrawn to the inferior vena cava. The inflation-deflation cycle took less than 15 seconds and the maximum pressure attained was 400 kPa (4 atm). The balloon position during the procedure was recorded on a cinematograph and the electrocardiogram and right ventricular and systemic arterial pressures were also recorded.

The right ventricular pressure rose to 90 mm Hg and the systemic pressure dropped to 50 mm Hg during balloon inflation. At the same time, bradycardia and extrasystoles developed. Examination of the recorded tracings showed complete heart block (fig 1b). The systemic pressure returned to the predilatation value and the right ventricular pressure fell to 50 mm Hg after deflation of the balloon. The catheter in the right ventricle was advanced to the pulmonary artery and a pullback showed a residual gradient of 25 mm Hg across the pulmonary valve.

In view of persisting complete heart block on electrocardiographic monitoring no further dilatation was attempted and the catheters and guide wire were removed. The patient was put on continuous electrocardiographic and blood pressure monitor. A tracing at four hours after the procedure still showed complete heart block with an atrial rate of 135/min and ventricular rate 75/min (fig 2b). The blood pressure was stable and the patient was symptom free. Twenty four hour Holter recording showed that the heart block was constant; the ventricular rate varied between 70 and 75 beats/min and there were no extrasystoles. A treadmill exercise test one week later showed no significant increase in ventricular rate after 15 minutes on the modified Bruce scale.

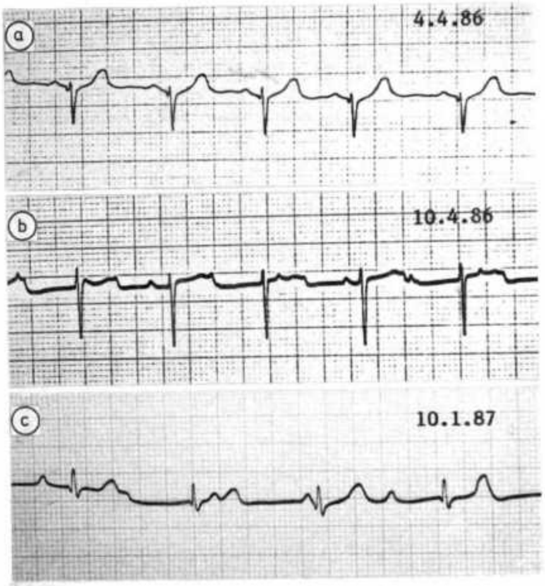

Fig 2 *Electrocardiogram taken (a) before, (b) four hours after balloon dilatation, and (c) nine months after balloon dilatation showing persistent complete heart block.*

The patient was followed up without any specific treatment. Follow up electrocardiograms at regular intervals showed persistent complete heart block (fig 2c).

Discussion

Transient arrhythmias are common during balloon dilatation of the heart valves and angioplasty. The most frequently reported abnormalities are extrasystoles during balloon inflation and transient bradycardia after balloon deflation.[2] Other arrhythmias include asymptomatic ventricular extrasystoles and accelerated idioventricular rhythm recorded on 24 hour Holter electrocardiogram during the first day after the procedure.[2-5] Conduction disturbances are rarely described. Tynan *et al* described a one month old child with dysplastic pulmonary valve who developed a complete heart block with a ventricular rate of 40/min during balloon dilatation that reverted spontaneously to normal rhythm after 120 seconds.[3] Transient prolongation of the QT_c interval was reported in most patients undergoing balloon dilatation for pulmonary stenosis, aortic stenosis, and coarctation of the aorta.[5] Prolongation of the QT_c interval might increase the risk of R-on-T phenomenon and hence serious ventricular arrhythmias. Late deaths attributable to ventricular fibrillation have been reported after balloon angioplasty for coarctation of the aorta.[5] The cause of the above conduction disturbances have not been determined.

The cause of the complete heart block in our patient was probably traumatic. The balloon (40 mm) may have been too long so that as it straightened during inflation its proximal segment directly impinged on the triangle of Koch and hence the atrioventricular node. The effect was more pronounced since a balloon that was relatively large for the patient's age was used. Direct pressure on the left bundle branch was thought to be the cause of the temporary left bundle branch block seen in patients undergoing balloon dilatation of an aortic stenosis. Permanent complete heart block has been produced after balloon dilatation of severely stenotic mitral valves.[6] Though no deleterious effects were reported by Radtke *et al*, who used balloons that were as much as 60% larger than the pulmonary annulus,[4] and Miller, who used uniformly large (18 mm) balloons for patients over one year old without measuring the pulmonary annulus from angiograms,[7] our case showed that oversized balloons can be hazardous. It would be safer to use shorter balloons and the cross sectional echocardiogram or larger reference markers other than the catheter to measure the pulmonary annulus.

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Pulmonary atresia with ventricular septal defect and coronary artery fistula: a late presentation

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SUMMARY A 41 year old man presented with cyanosis and progressive shortness of breath. Cardiac angiography showed absent central pulmonary arteries, ventricular septal defect, and a fistula between the left coronary artery and pulmonary artery. Most of the blood reaching the lungs came through this fistula. An attempt at surgical palliation was unsuccessful.

Obstruction of the right ventricle, right ventricular outflow tract, and pulmonary arteries was seen in about 25–30% of all congenital heart defects.[1] There is a range of abnormalities in pulmonary atresia with ventricular septal defect—from valve atresia to absent central pulmonary arteries (truncus type IV).[2] The course and presentation are varied and there are many surgical treatment options. These defects can present in the first few weeks of life as severe cyanosis and acidosis, as in those infants in whom the pulmonary flow is derived mainly through the ductus arteriosus, or in later life when patients outgrow their well developed aortopulmonary collaterals.

We report an unusual case of a man of 41 who, despite having no central pulmonary arteries, a ventricular septal defect, and a coronary artery-pulmonary artery fistula, had minimal symptoms.

Case report

A 41 year old man was referred to the Ibn Al Bitar Hospital, Baghdad with a history of progressive shortness of breath on exertion. He also had a recent episode of haemoptysis. There was no history of chest pain. He was of average build (weight 57 kg) and had central cyanosis and grade III clubbing. His pulse was 80 per minute with regular rhythm; his blood pressure was 120/80 mm Hg. There was a single second heart sound at the left sternal border with no murmurs. The haemoglobin concentration was 22 g/dl with a haematocrit of 65%. The electrocardiogram showed sinus rhythm with evidence of right axis deviation and right ventricular hypertrophy. The chest radiograph showed cardiomegaly with reticulation in both lung fields.

The patient underwent cardiac catheterisation and the measured oxygen saturations were as follows: superior vena cava 63%, inferior vena cava 72%, mid-right atrium 68%, right ventricular apex 65%, left ventricle 94%, and ascending aorta 85%. The pressure measurements were right ventricle 105/0–9 mm Hg, left ventricle 105/0–9 mm Hg, and ascending aorta 115/70 mm Hg. Angiography showed obstruction of the right ventricular outflow tract, no central pulmonary arteries, and a high ventricular septal defect. The aortic root injection showed a fistula between the coronary artery and pulmonary artery. Detailed coronary angiography showed a communication between the left circumflex coronary artery and the pulmonary arteries. Most of the blood reaching the lungs came through this fistula (figure).

With a view to disconnecting the fistula from the coronary circulation and constructing a modified Blalock-Taussig shunt, we performed an exploratory left anterolateral thoracotomy. At operation the fistula was isolated, but the distal main, left, and right pulmonary arteries were not found. Several small thin-walled communicating vessels were found at the hilum. Any attempt to find a larger vessel would have compromised these vessels and we had to abandon the procedure. The patient made a satisfactory recovery after the operation and was discharged home on the tenth postoperative day. He refused any further surgical treatment.

Discussion

The definitive repair for pulmonary atresia and ventricular septal defect is closure of the defect and construction of a right ventricular pulmonary artery continuity.[3-5] This can be performed as the primary

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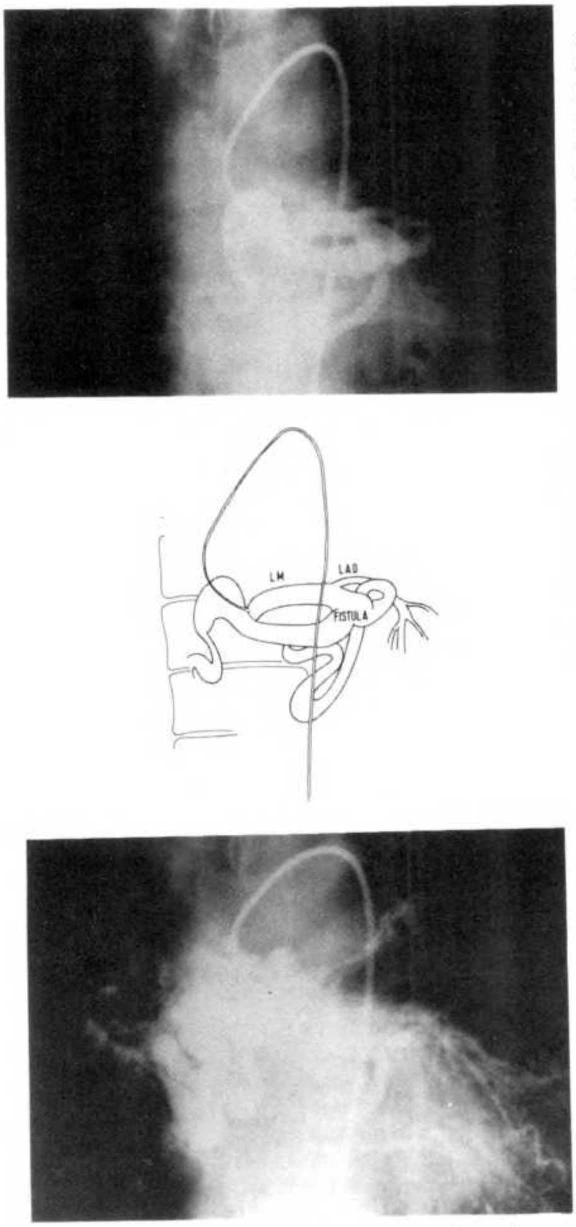

Fig *Left coronary artery angiogram showing the fistula arising from the circumflex coronary artery and filling the pulmonary circulation. LM, left main coronary artery; LAD, left anterior descending artery.*

procedure if the pulmonary artery is large enough or as a two stage procedure in which a systemic to pulmonary shunt is constructed to allow the pulmonary artery to grow. In patients with truncus type IV defect, the collateral vessels should be included in any attempt at correction.

The presence of a coronary artery-pulmonary artery fistula increases the risk of myocardial ischaemia. Life expectancy in these patients is further shortened by bacterial endocarditis, dissection embolisation and rupture of the fistula, or congestive cardiac failure and pulmonary hypertension. Early surgical intervention is recommended for this condition.[6-9]

In our patient there were no murmurs despite the coronary artery-pulmonary artery fistula. This was probably an indication of a considerable increase in pulmonary vascular resistance. Because of the features noted above and the longstanding cardiac defect in our patient, we planned only to disconnect the fistula from the coronary circulation and to reconstruct a pulmonary systemic shunt. The absence of a sizeable distal pulmonary artery, however, precluded any shunting. In the presence of adequate resources, he might be a candidate for cardiopulmonary transplantation. Nevertheless, he has survived 41 years with minimal symptoms while receiving pulmonary blood through the coronary artery fistula.

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Atrioventricular block complicating acute streptococcal tonsillitis

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SUMMARY A 38 year old woman presented with severe weakness, high fever, and sore throat. Physical examination showed follicular tonsillitis and bradycardia caused by a atrioventricular block. Within 24 hours a normal sinus rhythm was regained but slight transient ST-T changes compatible with myocarditis were evident. Throat culture grew *Streptococcus haemolyticus* group A.

Myocarditis is associated with various infections.[1] The involvement of the conduction system may cause disturbances such as first and second degree atrioventricular block and even complete heart block.[2] Different aetiological agents including viruses, spirochaetes, parasites, and bacteria can cause this severe complication.[1-3]

We report an instance of transient atrioventricular heart block in a patient with an acute streptococcal throat infection.

Case report

A 38 year old woman presented with a six hour history of severe weakness, fever of 39·5°C, and sore throat. Physical examination showed an irregular pulse of 60 beats per minute. The tonsils were swollen, red, and covered with white exudate, and there was submandibular tender lymphadenopathy.

The lungs were clear; a 2/6 systolic murmur was heard at the heart base. The liver and spleen were not enlarged, and there was no other lymphadenopathy.

Laboratory examination showed an erythrocyte sedimentation rate of 45 mm in the first hour; a haemoglobin concentration of 13·3 g/dl, white blood cell count 17 6000 × 10^9/l, and platelet count of 380 000 × 10^9/l. Kidney and liver function tests were all normal. Repeated measurements of plasma creatine kinase were all within the normal range. The antistreptolysin O titre rose from 160 units to 480 units and the test for C-reactive protein was negative. Throat culture grew *streptococcus haemolyticus* group A. An electrocardiogram an hour after admission showed atrioventricular block alternating with runs of complete atrioventricular block (fig 1). The echocardiogram was normal. She was treated with penicillin G (8 million units/day) and continuously monitored by electrocardiography.

Twenty four hours later normal sinus rhythm was restored but slight ST-T changes compatible with myocarditis developed (fig 2a). Two weeks later these changes had disappeared completely (fig 2b). A year later the patient was in good health.

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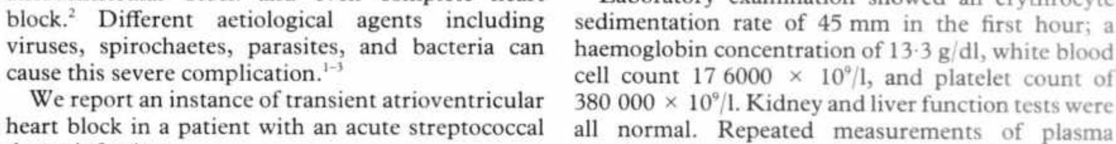

Fig 1 *Electrocardiographic recording on lead II at admission showing atrioventricular block.*

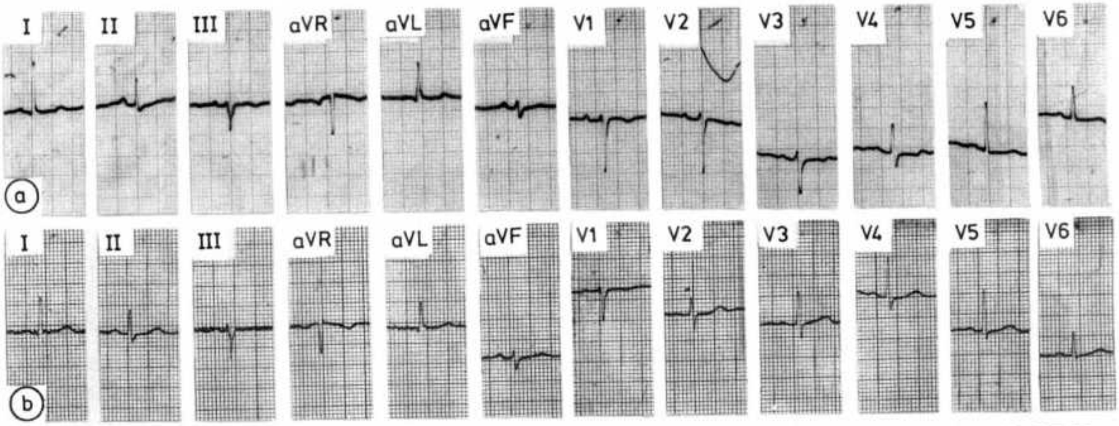

Fig 2 *(a) Twelve lead electrocardiographic recordings 24 hours after admission showing normal sinus rhythm with ST-T changes consistent with myocarditis. (b) Twelve lead electrocardiographic recordings 14 days after admission.*

Discussion

The association between streptococcal infection and cardiac damage in rheumatic fever is well known. There have been several studies of the incidence of myocarditis and conduction disturbances in the course of streptococcal tonsillitis or scarlet fever. Electrocardiographical changes compatible with myocarditis were seen in up to 39% of patients with scarlet fever.[3-5] Only one case of complete heart block was reported among 2831 cases of scarlet fever.[4] This prompted some workers to say that "the possibility of complicating rheumatic fever should be raised whenever conduction defect appears 2–3 weeks after the initiation of streptococcal infection".[5]

No atrioventricular conduction disturbances were found in 51 patients with an acute streptococcal infection.[6] Only one case of complete heart block was reported in association with follicular tonsillitis and even in this patient the existence of occult rheumatic fever could not be ruled out.[7] An additional five cases with complete heart block and a significant increase in antistreptolysin O titres were reported, but in these cases the clinical and bacteriological findings did not support the diagnosis of acute streptococcal infection.[8 9]

The discrepancy between the changes typical of mild myocarditis and the atrioventricular and complete heart block in our case deserves special attention. Reports of similar findings in previous cases suggested the possibility of selective injury to the conduction system of the heart.[6 8 9] One possible explanation for this is that the cells in this system contain more glycogen than the heart muscle cells.

The occurrence of rheumatic fever after streptococcal infection is usually attributed to allergic immunological reaction. Whereas the transient appearance of the myocarditis and atrioventricular heart block early in the course of infection in our case are more likely to be caused by a streptococcal toxin.

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Congenital left atrial wall aneurysm in a patient with neurofibromatosis

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SUMMARY A congenital intrapericardial aneurysmal dilatation of the left atrial wall was found in a 28 year old man who presented with atrial fibrillation after a syncopal event. The patient had cutaneous manifestations of neurofibromatosis. The diagnosis was made by cross sectional echocardiography and confirmed by angiocardiography. Surgical excision of the aneurysm resolved the symptoms.

Congenital intrapericardial aneurysm of the left atrium is a rare anomaly. There are 32 reports of aneurysms affecting the atrial appendage alone[1-8] and 13 reports of aneurysms of the atrial wall.[9-11] We report a case in which there was an intrapericardial aneurysm of the left atrial wall and we review the mode of presentation, investigation, potential complications, and possible association with neurofibromatosis.

Case report

A 28 year old man presented to a local hospital after a syncopal episode associated with tight central chest pain and severe dyspnoea while playing football. On

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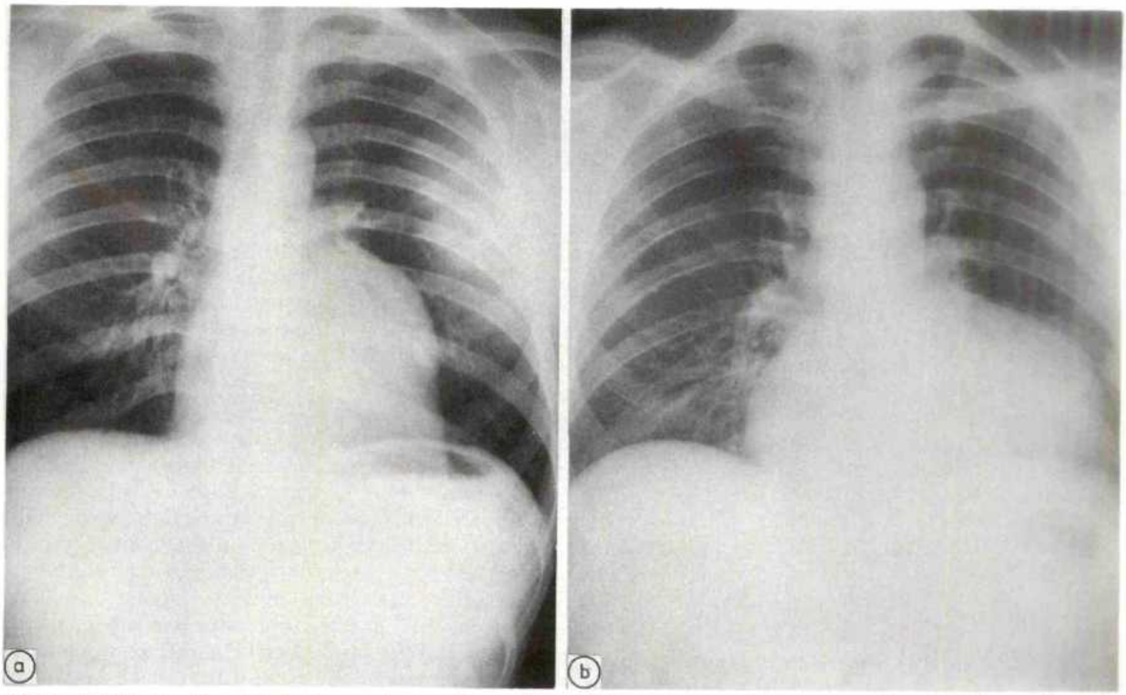

Fig 1 *(a) Chest radiograph showing an abnormally prominent left heart ten years before presentation. (b) Chest radiograph showing cardiomegaly at presentation.*

arrival he was conscious but hypotensive, and electrocardiographic monitoring showed atrial flutter with variable block. When the arrhythmia was found to be resistant to cardioversion and intravenous amiodarone he was transferred to the regional cardiothoracic centre.

He reported increasing exertional dyspnoea over the past two months. There was no recent history of viral illness or a family history of cardiovascular disease.

He was clinically in atrial fibrillation with a ventricular rate of 160 per minute but there was adequate perfusion with a blood pressure of 100/60 mm Hg. A pulsation was seen in the pulmonary area and the apex was not displaced. The jugular venous pulse was not elevated. Heart sounds were normal with a soft ejection systolic murmur at the left sternal edge. Lung fields were clear. He had seven café au lait spots and bilateral axillary freckling.

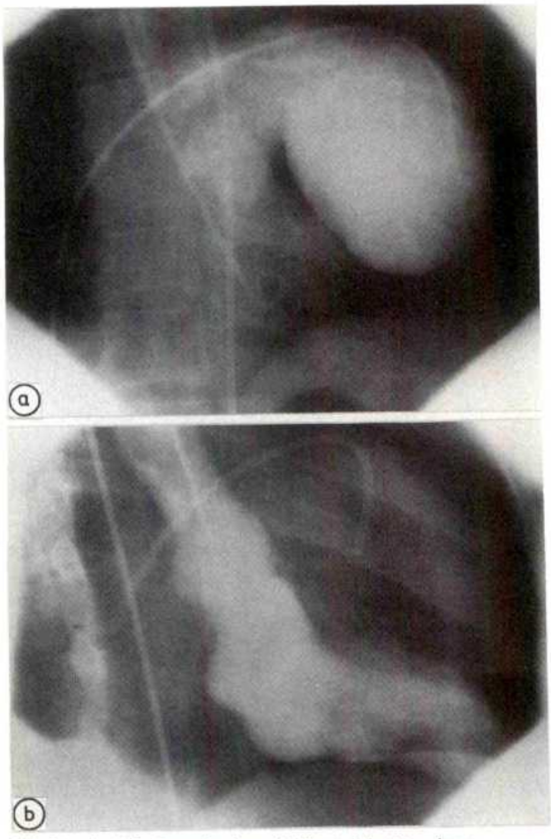

Fig 2 *(a) Catheterisation of left atrial appendage aneurysm via the patent foramen ovale. (b) Left ventricular angiogram showing compression of left ventricle by left atrial aneurysm.*

The 12 lead electrocardiogram confirmed atrial fibrillation and showed right axis deviation, partial right bundle branch block, poor R wave progression, and deep S waves in V2 and V3. A chest radiograph obtained 10 years before showed an abnormality of the mid left heart border (fig 1a). The chest radiograph at presentation showed considerable cardiomegaly with a cardiothoracic ratio of 19:30 (fig 1b). Cross sectional echocardiography showed normal left ventricular size and function. Adjacent to and impinging on the left ventricle was a large echo-free chamber. Doppler examination confirmed flow within the chamber and colour Doppler suggested that it communicated with the left atrium close to the mitral valve. Cardioversion with energies up to 400 J was attempted but failed. Treatment with digoxin improved the control of ventricular rate and symptoms.

Right heart catheterisation showed normal pressures and no intracardiac shunt but the left atrium and the additional chamber were entered through a patient foramen ovale. Injection of contrast confirmed communication between the chamber and the left atrium (fig 2a), and the left ventricular angiogram suggested compression of the left ventricle during diastole, presumably by the large aneurysm (fig 2b).

A dilated aneurysm of the left atrial wall with a maximum diameter of 8 cm was found at operation through a left thoracotomy. Electrophysiological studies showed electrical activity in all areas of the aneurysm. The left atrial appendage was normal. The aneurysm was resected without cardiopulmonary bypass. Post-cardiotomy syndrome developed and lasted three days and subsequent cardioversion restored sinus rhythm.

Histological examination showed fibrosis in the aneurysm wall mainly of the subendocardium but with residual irregular myocardial fibres, many of which were hypertrophied. Neural fibres were present and normal, in keeping with the finding of electrical activity within the aneurysm.

Discussion

Congenital aneurysms of the left atrium are rare and fall into four distinct pathological groups: intrapericardial aneurysm of the left atrial wall; intrapericardial aneurysm of the left atrial appendage; herniation of the left atrial appendage through a congenital pericardial defect (not strictly an aneurysm)[12-14]; and multiple saccular aneurysms of the left (and right) atrial wall.[15] More rarely, congenital aneurysms of the right atrium have been described[16 17]; in one case there was also an aneurysm of the left atrial wall.[18]

Table *A comparison of reported findings in aneurysms of the left atrial wall and appendage*

	Left atrial	
Patient characteristics	*Wall aneurysm No (%)*	*Appendage aneurysm No (%)*
Case reports	14 (100)	32 (100)
Clinical features:		
Palpitation/SVT	10 (71)	16 (50)
Chest pain	2 (14)	4 (13)
Systolic murmur	8 (57)	10 (31)
Systemic embolism	0 (0)	8 (25)
Electrocardiogram:		
Atrial fibrillation/SVT	4 (29)	9 (28)
Chest radiograph:		
Mid left heart bulge	3 (21)	22 (69)
Cardiomegaly	11 (79)	10 (31)
Operative findings:		
Mural thrombus	1 (7)	4 (13)

SVT, sustained ventricular tachycardia.

The table summarises findings reported in aneurysms of the left atrial wall and appendage. Aneurysms are equally common in male and female patients aged 1–69 years. Aneurysms of the left atrial wall usually arise from the posterior wall and may extend to the mitral ring. There are three reports of the aneurysm affecting the entire left atrium.[9 18] Aneurysms of the left atrial appendage usually have a narrow neck and are separate from a normal sized left atrium. As in our patient, paroxysmal or sustained atrial arrhythmia is the usual mode of presentation. A routine chest radiograph is often the first indication of cardiac disease in a symptom free patient. Occasionally, the condition presents as atypical chest pain. Intraventricular conduction defects and T wave abnormalities have been described.[8] The chest radiograph is always abnormal (table). A discrete bulge in the mid left heart in a symptom free patient is also the usual presentation when there is herniation of the left atrial appendage,[13] but there are isolated reports of chest pain, pericarditis, and strangulation of the appendage.[14]

Clinical differentiation between the aneurysms may be difficult. Cross sectional echocardiography may show congenital pericardial defects[8 12] and exclude extracardiac causes for the abnormal cardiac shadow. In this case combined echocardiographic and Doppler examination confirmed communication of the aneurysm with the left atrium but we were unable to distinguish between an aneurysm of the atrial wall or the atrial appendage. Radionuclide blood pool scanning[5] and computed tomography may be useful. Cardiac catheterisation with angiography has been most widely used to establish a definitive diagnosis.

The major risk of an aneurysm of the left atrial appendage is systemic (usually cerebral) embolism (table). None of the 13 patients with aneurysms of the atrial wall had systemic emboli, although at operation one had a thrombus in the aneurysm. It seems advisable to recommend anticoagulants in both groups at diagnosis in view of the risk of cerebral embolism.

It is not surprising that atrial arrhythmias are common in view of the fibrosis, hypertrophy, and dilatation of the atrial wall. As with previous reports, restoration of sinus rhythm was difficult and was only possible after the aneurysm had been resected. Operation is the recommended treatment because it also abolishes symptoms and removes the source of emboli.[1] Operation is recommended for extrapericardial herniations because of the risk of strangulation.[12] To date there has been no reported mortality related to operation.

The assertion that intrapericardial aneurysms are congenital is based on pathological examination and the association with other cardiac anomalies.[11] The aneurysmal dilatation is thought to be the result of congenital weakness in the wall. Hypertrophy of the atrial myocardium with a thickened endocardium or the development of fibroelastosis has been reported.[10]

To our knowledge, this is the first reported case of left atrial aneurysm and neurofibromatosis. The presence of seven café au lait spots and bilateral axillary freckling is pathognomic of neurofibromatosis. There was no family history of the disease; however, new mutations account for 50% of all index cases. Close clinical examination did not find any other manifestations of the disease. In one series 7·7% of children with neurofibromatosis had congenital heart disease.[19] A strong association between neurofibromatosis and pulmonary valve stenosis has been described.[20] Large series have suggested that the association between neurofibromatosis and congenital heart disease is coincidental. Because neurofibromatosis is often not diagnosed until the third decade, however, a true association might have been overlooked.

We thank Dr Douglas Reid and Mr Colin J Hilton for their help and for permission to report this case.

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Correspondence

Haemodynamic observations during percutaneous transluminal coronary angioplasty in the presence of synchronised diastolic coronary sinus retroperfusion

Sir,
We should like to comment on the important study of Beatt *et al* (1988);**59**:159–67. The development of new intracoronary interventions to protect jeopardised myocardium is a goal we share with Beatt *et al*. The Rotterdam team used a similar protocol and similar criteria for evaluating the possible beneficial effects of synchronised coronary sinus retroperfusion to the ones that we are currently using. We agree with their criticism of the equipment that they used and we would like to draw attention to the improved techniques of retroperfusion and retroinfusion developed during the past two years.[1]

They report that the method of retroperfusion that they used did not produce any convincing clinical benefit during acute myocardial ischaemia. It seems that the retroperfusion delivery equipment that they used is essentially the same system (Model EC-1) that we helped to develop but abandoned three years ago.

Beatt *et al* question the discrepancy between reports of obvious benefits in animal studies and those of failure in human studies. They do not indicate the weight and size of their patients but we assume that they were several times heavier than the dogs used in the animal studies. The limited volume of blood that was pumped retrogradely into the coronary veins might have been adequate in dogs but was probably insufficient in human beings. The autoinflatable balloon has a considerable negative effect on the net flow because blood is needed to fill the balloon on each pump cycle. The volume of the 10 mm balloon reportedly used in their study probably reduced net flow by at least 40–70 ml/min. Nevertheless, in a larger study, investigators from the University of Massachusetts reported favourable results with the same system.[2]

We are currently using equipment manufactured by Retroperfusion Systems, Inc (RSI) of Costa Mesa, California, which incorporates many major improvements in design that should overcome the deficiencies referred to in the Rotterdam article. The dual lumen 8 F catheter that we are currently using has an infusion lumen with a cross sectional area greater than twice the reported cross sectional area (56 mm) of the catheter described in the Rotterdam study. The second lumen of the new catheter monitors coronary venous pressure. This catheter system can also deliver significantly greater flows because it is designed to prevent wasteful regurgitation of oxygenated blood during the pump filling stroke (down stroke).

Moreover, unpublished studies of the RSI system in 12 patients in Rouen, France, and eight patients in Los Angeles, California, yielded positive results when retroperfusion was used to support the ischaemic myocardium during percutaneous transluminal coronary angioplasty (with left ventricular function measured by cross sectional echocardiography as the major end point for efficacy).

One patient in the Los Angeles series developed sudden akinesis of the left ventricular septum and anterolateral wall, resulting in cardiogenic shock, when acute coronary artery dissection occurred during percutaneous transluminal coronary angioplasty. Retroperfusion was started immediately and within seconds the intense anginal pain vanished. Within a few minutes left ventricular function improved, blood pressure increased, and the patient was considered sufficiently stable to permit attempts to reopen the occluded artery with retroperfusion support. Retroperfusion was maintained for two hours and 30 minutes until emergency bypass surgery could be performed. The patient had an uneventful recovery and within a week was discharged without significant wall motion abnormality.

We feel we must answer the remark of the Rotterdam group who state that with retroperfusion "delivery of thrombolytic and antiarrhythmic agents is unlikely to be substantially more effective than intravenous administration." Many animal and some human studies have shown that the coronary venous channel can effectively deliver cardioactive agents even when the coronary arteries are occluded.[3–7] Moreover, high myocardial drug concentrations, up to 100 times that measured in the normal myocardium, were obtained with retroinfusion of the coronary venous channels with dosages much lower than those normally required for systemic infusion. Therefore, we believe that retroinfusion will be an important additional technique in clinical cardiology.

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Notices

British Cardiac Society

The Annual General Meeting for 1988 will take place in Belfast on 23 and 24 March 1988, and the closing date for receipt of abstracts was 4 January 1988.

Cardiology—Moroccan, French, American meeting

An International Congress of Cardiology, co-sponsored by the Council on Clinical Cardiology of the American Heart Association, will be held in Marrakesh on 2 to 5 November 1988. Further information from: Dr M Benomar, Ligue Nationale de Lutte Contre les Maladies Cardiovasculaires, B P 1326, Rabat R P, Morocco; Dr Y Grosgogeat, Groupe Hospitalier Pitié-Salpétrière, Service de Cardiologie, 47 Boulevard de l'Hôpital, 75013 Paris, France; Dr W C Sheldon, The Cleveland Clinic Foundation, Department of Cardiology, 9500 Euclid Avenue, Cleveland, Ohio 44106, USA.

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